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Recent progress in Lewis acid–Lewis base bifunctional asymmetric catalysis*

Motomu Kanai‡,[1,2], Nobuki Kato[2], Eiko Ichikawa[2], and Masakatsu Shibasaki[1]

[1]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113–0033, Japan; [2]PRESTO, Japan Science and Technology Corporation (JST), 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Abstract: Two enantioselective cyanation reactions, the Strecker reaction of ketoimines and the Reissert reaction of pyridine derivatives, promoted by Lewis acid–Lewis base bifunctional asymmetric catalysts are described.

Keywords: Bifunctional asymmetric catalysis; cyanation; Strecker reaction; ketoimines; Reissert reaction; asymmetric catalysis.

INTRODUCTION

Catalytic enantioselective reactions are a very powerful synthetic method [1]. Current challenges focus on the development of enantioselective catalysts with high activity and broad substrate generality, which leads to a practical, efficient, and environmentally friendly chemical synthesis. Toward this goal, basic conceptual advances in catalyst design are very important. Our basic concept is the asymmetric bifunctional catalysis (Fig. 1, **1**) [2]. If an asymmetric catalyst activates both electrophilic (substrate 1 in Fig. 1, **1**) and nucleophilic (substrate 2) substrates at the positions defined by the two functionalities of the catalyst (dual activation), high enantioselectivity should be obtained. On this basis, we selected a combination of Lewis acids and Lewis bases to target cyanation reactions of carbonyl compounds and their derivatives, such as aldehydes, ketones, and imines. We expected the Lewis acid moiety of our bifunctional catalyst to activate the electrophile and the Lewis base moiety to activate trimethylsilyl cyanide (TMSCN) through interactions with a vacant orbital of the silicon atom. We developed two enantioselective catalysts using either BINOL or carbohydrates as a scaffold for the two functionalities. The aluminum complex of BINOL-derived ligand **2** produced high enantioselectivity and substrate generality for the cyanosilylation of aldehydes [3], the Strecker reaction of aldimines [4], and the Reissert reaction of quinolines and isoquinolines [5]. On the other hand, D-glucose-derived ligands **3** and **4** complexed with titanium or lanthanide metals promoted general catalytic enantioselective cyanation of ketones [6] and ketoimines [7]. In this manuscript, we describe recent progress in this field; specifically, the catalytic enantioselective Strecker reaction of ketoimines with broad substrate generality and high catalyst turnover [8], and the first catalytic enantioselective Reissert reaction of pyridine derivatives [9].

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‡Corresponding author

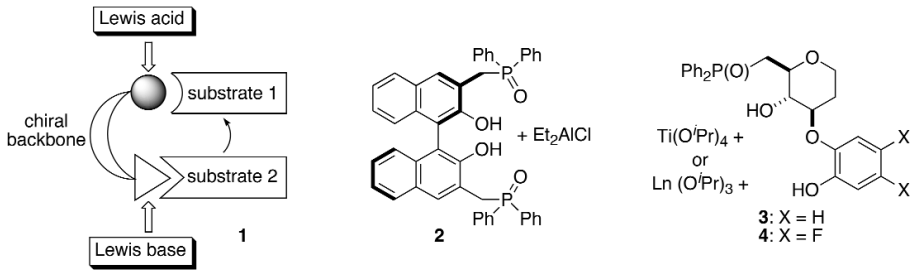
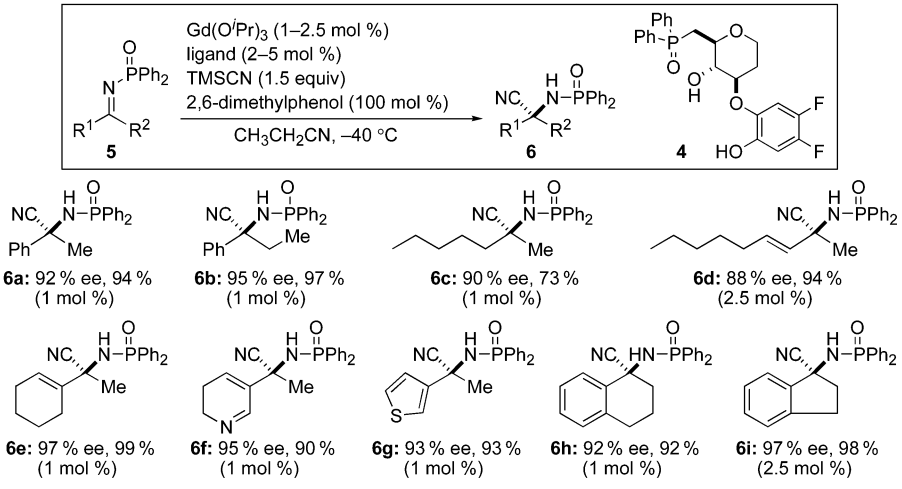


Fig. 1 General concept of Lewis acid–Lewis base bifunctional asymmetric catalysis (**1**) and asymmetric catalysts developed in our group in this category.

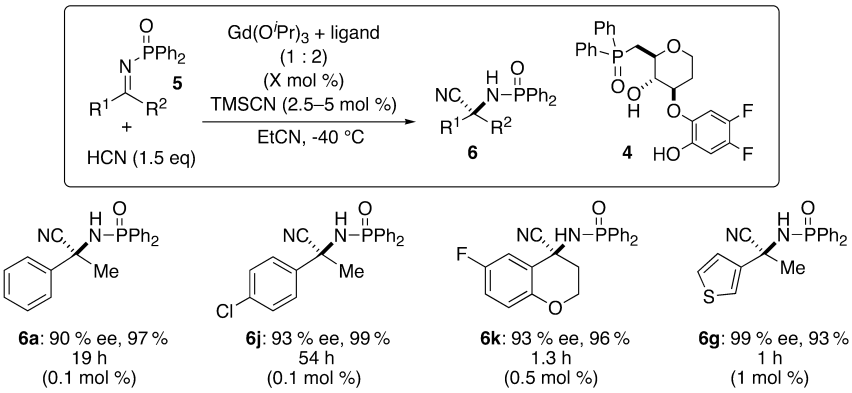
CATALYTIC ENANTIOSELECTIVE STRECKER REACTION OF KETOIMINES

Chiral α,α-disubstituted α-amino acids are important building blocks for pharmaceuticals and artificially designed peptides [10]. The catalytic enantioselective Strecker reaction of ketoimines is one of the most direct and practical methods for the synthesis of this class of compounds [11]. Jacobsen and Vachal developed a unique organocatalyst that promotes reactions with aryl methyl and *tert*-butyl methyl ketoimines [12]. Vallée et al. reported a reaction with an acetophenone-derived ketoimine, catalyzed by a chiral heterobimetallic complex [13]. We also reported a reaction with *N*-phosphinoyl ketoimines using a catalyst prepared from $Gd(O^iPr)_3$ and D-glucose-derived ligand **4** in a 1:2 ratio [7]. Despite these contributions, substrate generality and catalyst loading can still be improved. Recently, we observed that both catalyst activity and enantioselectivity improved greatly using 2,6-dimethylphenol as a stoichiometric additive. Thus, the catalytic enantioselective Strecker reaction of ketoimines with a broad substrate generality was developed (Scheme 1) [8a].



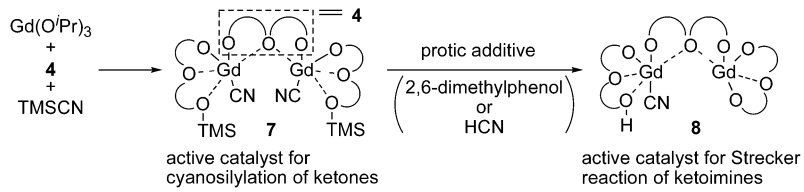
Scheme 1 Catalytic enantioselective Strecker reaction of ketoimines using 2,6-dimethylphenol as an additive.

Furthermore, we successfully developed an atom-economical process using HCN as both a proton source and a stoichiometric cyanide source [8b]. Thus, the reaction proceeded smoothly in the presence of a catalytic amount of TMSCN and a stoichiometric amount of hydrogen cyanide (HCN) (Scheme 2). The loading of the asymmetric catalyst was minimized to as low as 0.1 mol % in the optimum case under these conditions. A catalytic amount of TMSCN was essential for the reaction to proceed.



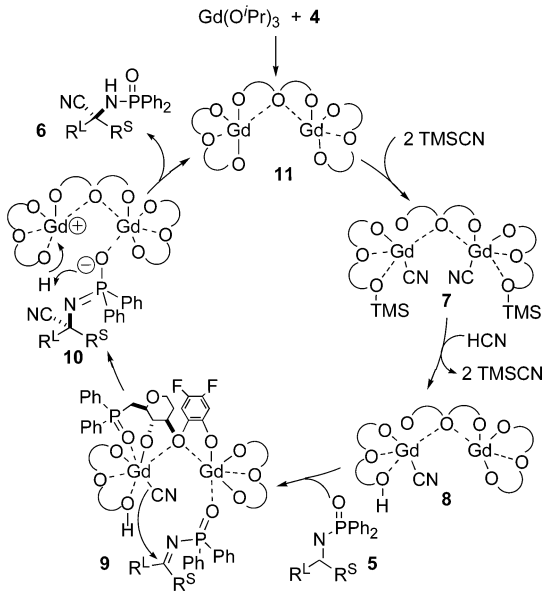
Scheme 2 Catalytic enantioselective Strecker reaction of ketoimines using a catalytic amount of TMSCN and a stoichiometric amount of HCN.

Because a protic additive (2,6-dimethylphenol or HCN) improves the enantioselectivity as well as the catalyst activity, we expected that the additive should change the active catalyst structure. This expectation was supported by structural studies of the active catalyst using electrospray ionization mass spectrometry (ESIMS). First, the mass peak corresponding to a 2:3 complex of gadolinium cyanide and the silylated ligand (**7**) was observed in the absence of 2,6-dimethylphenol. This observation was consistent with the previous studies using **3** as a chiral ligand for catalytic cyanosilylation of ketones [6c]. When 2,6-dimethylphenol was added to the solution, this original peak disappeared and new peak corresponding to a 2:3 proton-containing complex **8** was observed (Scheme 3). We believe that complex **8** is the actual asymmetric catalyst for the Strecker reaction.



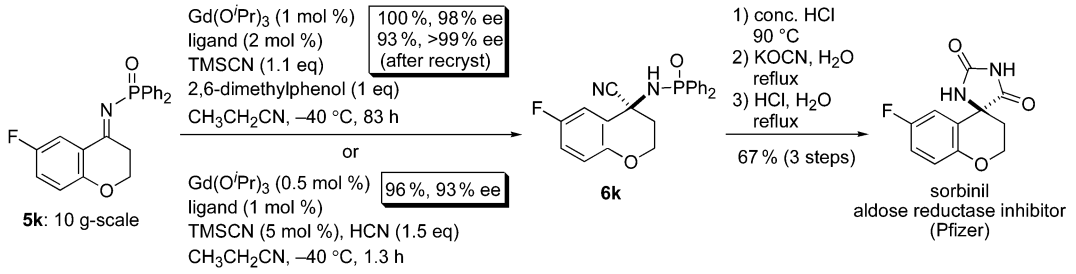
Scheme 3 Preliminary studies of catalyst structure: proton-containing 2:3 complex **8** as an active enantioselective catalyst for the Strecker reaction of ketoimines.

Based on these observations, we proposed a catalytic cycle as shown in Scheme 4. To the active catalyst **8**, the substrate ketoimine **5** is incorporated. An intramolecular cyanide transfer from the gadolinium cyanide to the activated substrate should define the enantioselectivity (**9**). Here, the bimetallic complex plays multiple roles; a gadolinium atom works as a Lewis acid to activate a ketoimine, a gadolinium cyanide works as a nucleophile, and the phosphine oxide works as a Lewis base to activate the nucleophile. The positions of these functionalities are defined by the chiral ligand, thus producing high enantioselectivity. The zwitter ionic intermediate **10** should be generated after the cyanation step. This intermediate collapses through an intramolecular proton transfer to release the product **6** and the gadolinium alkoxide complex **11**. From **11**, successive reactions with TMSCN and HCN reproduce the active catalyst **8**. The fact that a catalytic amount of TMSCN was essential even when using HCN as a stoichiometric cyanide and proton source suggests that **8** should be regenerated only through the silylated 2:3-complex **7**, and direct protonolysis of the alkoxide complex **11** by HCN does not occur.



Scheme 4 Proposed catalytic cycle for the enantioselective Strecker reaction of ketoimines.

Practicality of the catalytic enantioselective Strecker reaction was demonstrated by the application to an efficient synthesis of sorbinil, a potent aldose reductase inhibitor [14] (Scheme 5). The Strecker reaction of **5k** proceeded with excellent enantioselectivity using 1 mol % catalyst in the presence of 1 equiv of 2,6-dimethylphenol, or using 0.5 mol % TMSCN in the presence of 0.5 mol % TMSCN and 1.5 equiv HCN. The reaction was performed on a 10-g scale without any difficulty. Single recrystallization of the crude mixture produced enantiomerically pure **6k**. Acid hydrolysis followed by hydantoin formation gave sorbinil in high overall yield.



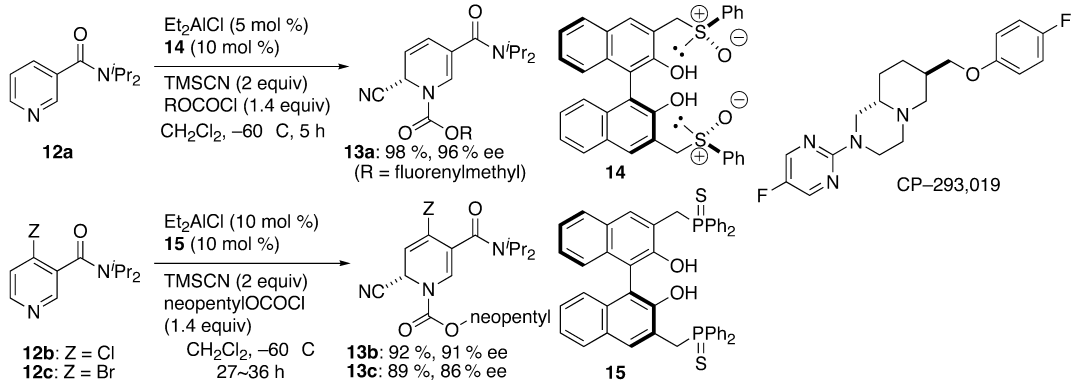
Scheme 5 Catalytic asymmetric synthesis of sorbinil.

CATALYTIC ENANTIOSELECTIVE REISSERT REACTION OF PYRIDINE DERIVATIVES

Chiral piperidines are among the most important building blocks for biologically active molecules and natural products. Many synthetic methodologies have been developed to access these useful heterocyclic compounds [15]. Among them, nucleophilic asymmetric addition to activated pyridine derivatives such as *N*-acyl pyridinium salts is a direct and attractive method. This type of reaction was developed, however, using stoichiometric amounts of chiral controllers and highly active organometallics such as Grignard or organocopper reagents as nucleophiles [16].

We successfully developed the first catalytic enantioselective Reissert reaction of pyridine derivatives through identification of new Lewis acid–Lewis base bifunctional asymmetric catalysts derived

from **14** and **15**, containing either chiral sulfoxides or phosphine sulfides as Lewis bases (Scheme 6) [9]. Thus, using a catalyst generated from Et_2AlCl and **14** in a 1:2 ratio (5 mol %) and FmocCl as an acylating reagent, product **13a** was obtained with excellent regio- and enantioselectivity (regioselectivity = 50:1). The selectivity was strongly dependent on the ratio of Et_2AlCl/ligand and the stereochemistry of the sulfoxides. If the catalyst was prepared from a 1:1 ratio of Et_2AlCl and **14**, product was obtained with low enantioselectivity as a mixture of regioisomers (1:1~2:1). Unsatisfactory results were also obtained using C_2-symmetric ligands with different stereochemistry on the sulfoxide. For other substrates containing halides at the 4-position (**12b** and **12c**), a phosphine sulfide-containing catalyst prepared from Et_2AlCl and **15** in a 1:1 ratio produced better results than using the catalyst derived from ligand **14**; using neopentyl chloroformate as an acylating reagent, products **13b** and **13c** were obtained in 92 and 89 % yield with 91 and 86 % ee, respectively.



Scheme 6 Catalytic enantioselective Reissert reaction of pyridine derivatives.

The reaction was applied to a catalytic enantioselective synthesis of CP-293,019, a dopamine D_4 receptor selective antagonist [17]. Although the origin of the high regio- and enantioselectivity of those new asymmetric bifunctional catalysts is currently under investigation, we believe that a dual activation of an acyl pyridinium intermediate and TMSCN by the aluminum atom and the Lewis base of the asymmetric catalyst should play a key role.

ACKNOWLEDGMENT

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