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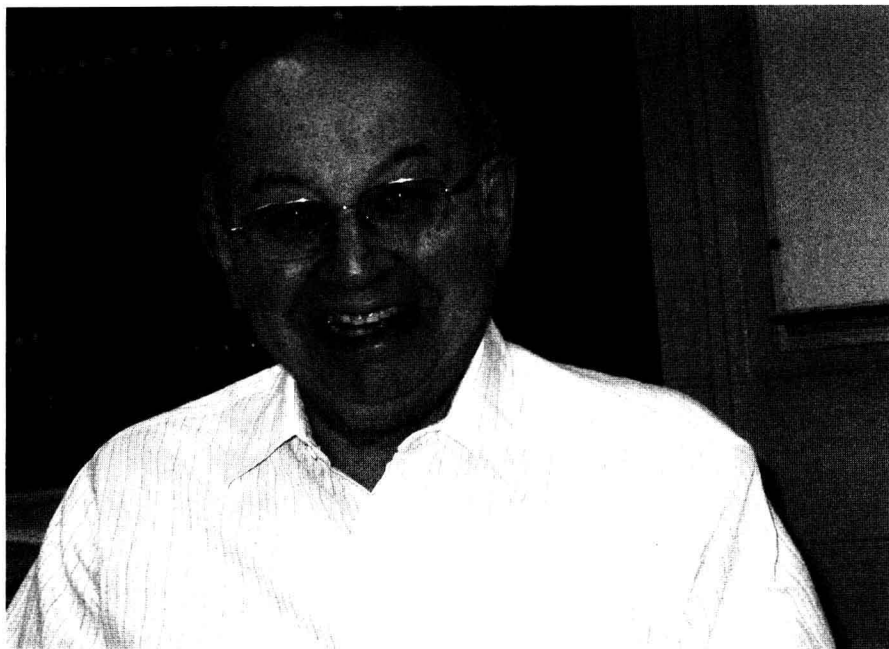
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Organic Reactions is delighted to dedicate volume 70 to Leo Paquette, Distinguished University Professor at The Ohio State University, in recognition of his nearly 30 year involvement with *Organic Reactions*.

Leo Paquette joined the Board of Editors of *Organic Reactions* in 1979, serving as Editor-In-Chief from 1989–1999. When Leo stepped down as a member of the Editorial Board in 1999, *Organic Reactions* was fortunate that he continued to serve as a member of the Board of Directors. As Editor-In-Chief, Leo was responsible for doubling the frequency of publication of *Organic Reactions*, from approximately one to two volumes per year. Leo's energy, wisdom, good cheer, and encyclopedic knowledge of organic chemistry will be missed by all associated with *Organic Reactions* as he steps down at the end of this year from the Board of Directors.

Larry E. Overman
Editor-In-Chief
December 13, 2007

PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry, the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Synthesis*, they have not been subjected to careful testing in two or more laboratories.

Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy, the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

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CHAPTER 1

THE CATALYTIC ASYMMETRIC STRECKER REACTION

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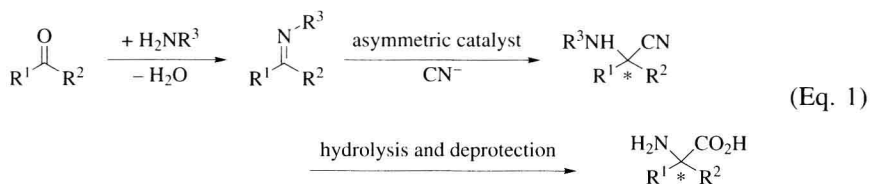
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INTRODUCTION

α -Amino acids are important building blocks for proteins, peptides, and pharmaceuticals. Among a wide variety of methods to synthesize optically active α -amino acids,^{1–6} the Strecker reaction⁷ is one of the simplest and the most powerful. This reaction consists of three steps (Eq. 1): (1) condensation of an aldehyde or a ketone with an amine to produce an imine, (2) nucleophilic attack of cyanide on the imine to produce an amino nitrile, and (3) hydrolysis of the amino nitrile to the corresponding α -amino acid. These three steps can be conducted in one pot. Conversion of the nitrile group to amide, amine, or aldehyde functionalities is also possible.



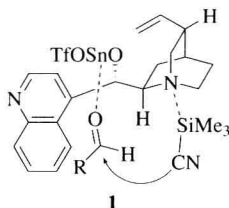
The catalytic promotion and enantiocontrol of cyanide addition to imines is the main focus of the catalytic asymmetric Strecker reaction. Therefore, isolated and purified imines are normally used as substrates. The catalyst turnover efficiency and enantioselectivity of this step are intimately related to the electronic and steric characteristics of the substrate imines, with the nitrogen substituent greatly contributing to these factors. However, since optically active α -amino acids are generally the synthetic target of a catalytic asymmetric Strecker reaction, the accessibility of the starting imines and ease of final deprotection of the product are also important considerations.

Due to the importance of catalytic enantioselective Strecker reactions, there have been several reviews on this topic to date.^{8–10} This chapter focuses on catalytic enantioselective Strecker reactions (and Reissert reactions) and the Tables cover all of the references through August 2007. For enzymatic reactions, the reader is directed elsewhere.¹¹

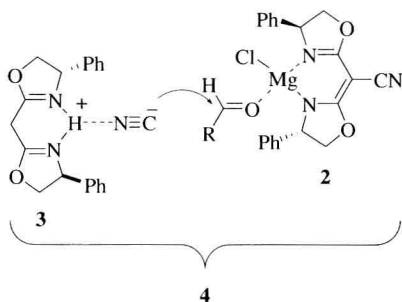
MECHANISM AND STEREOCHEMISTRY

Many of the catalysts for the asymmetric Strecker reaction (and the Reissert reaction) appear to promote the reaction through dual activation^{12–15} of the

electrophilic imine and the nucleophilic cyanide, either trimethylsilyl cyanide (TMSCN) or hydrogen cyanide (HCN).¹⁶ This type of asymmetric catalysis was initially postulated in the closely related catalytic asymmetric cyanosilylation of aldehydes. A dual activation mechanism was first proposed for chiral tin (II)–cinchonine catalyst **1**.¹⁷ In this reaction, the alkoxytin triflate and the tertiary amine of the quinuclidine are believed to act as a Lewis acid to activate the aldehyde, and as a Lewis base to activate TMSCN, respectively. Although high enantioselectivity (90% ee) was obtained, the catalyst turned over only twice (catalyst loading = 30 mol%, product yield = 63%), and the result for only one substrate (cyclohexanecarboxaldehyde) was reported.

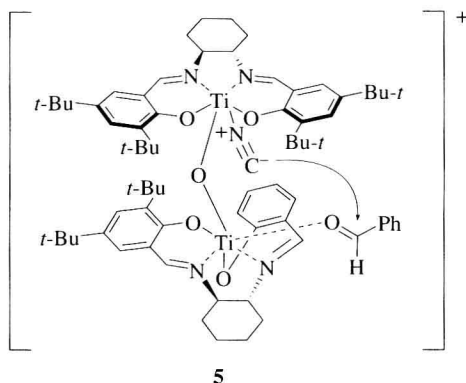


A synergistic combination catalyst was reported for an enantioselective cyanosilylation of aldehydes. Magnesium bisoxazoline **2** acted as a chiral Lewis acid to activate the aldehyde, and uncomplexed bisoxazoline **3** as a Brønsted base to activate HCN as shown in complex **4**.¹⁸ HCN was generated in a catalytic amount from TMSCN and moisture, and regenerated after TMS trapping of the intermediate cyanohydrin by TMSCN. Only aliphatic aldehydes produced high enantioselectivities in this report.

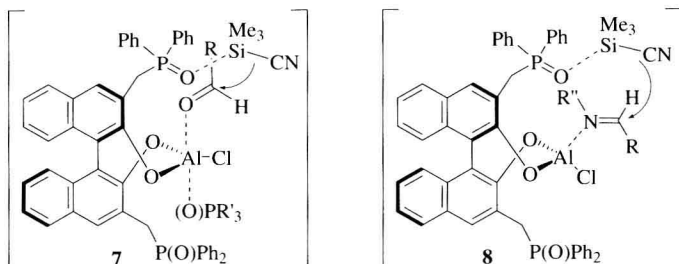
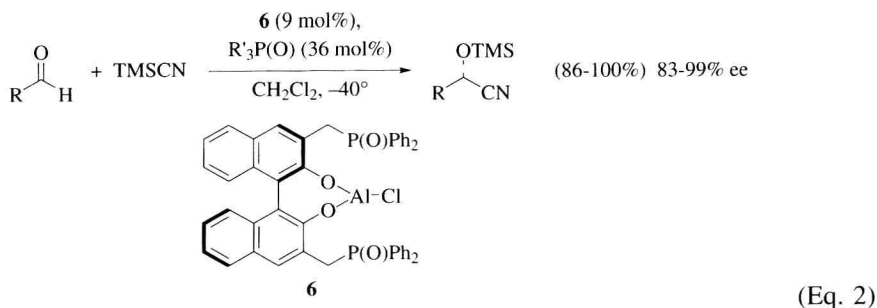


Extensive mechanistic studies of an asymmetric cyanosilylation of aldehydes and ketones catalyzed by a salen–titanium complex revealed that the actual catalyst is a bimetallic complex bridged by a μ -oxo atom (**5**).^{19,20} One titanium atom acts as a Lewis acid to activate the substrate, while the other titanium atom

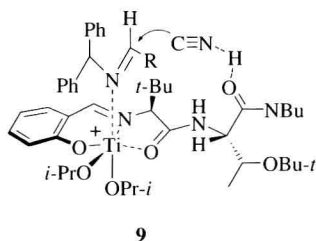
generates titanium cyanide (or isocyanide) via transmetalation with TMSCN. It was proposed that the reaction proceeds through an intramolecular cyanide transfer from one titanium to the substrate activated by the other titanium (**5**).^{21,22} Only aromatic aldehydes led to high enantioselectivity.



Asymmetric catalyst **6** (prepared from Et_2AlCl and the corresponding BINOL-derived ligand) promotes cyanosilylation of aromatic and aliphatic aldehydes with excellent enantioselectivities (Eq. 2).^{23,24} This catalysis is believed to occur via a dual activation mechanism, in which the aluminum provides a Lewis acidic site to activate the aldehyde and the internal phosphine oxide acts as a Lewis base to activate TMSCN as in intermediate **7**. The additive phosphine oxide ($\text{R}'_3\text{PO}$) coordinates to the aluminum, and modulates the Lewis acidity and geometry of the aluminum to be optimal for the dual activation pathway. This mechanism was supported by the following: (1) the reaction rate increased according to the electron density of the internal phosphine oxide (a nucleophile activator) at the 3,3'-positions of the BINOL scaffold, (2) an IR absorption derived from the activated ionic cyanide was observed ($\nu = 2057\text{ cm}^{-1}$; cf. TMSCN, $\nu = 2192\text{ cm}^{-1}$)²⁵ when the bifunctional catalyst **6** was mixed with TMSCN, while a monofunctional Lewis acid aluminum catalyst (generated from BINOL and Et_2AlCl) did not produce this absorption, and (3) a control reaction with a monofunctional catalyst containing diphenylmethyl groups at the 3,3'-positions of BINOL, instead of the Lewis basic phosphine oxide, produced the enantiomer of the products that were obtained using the bifunctional catalyst **6**. Catalyst **6** was later applied to a catalytic enantioselective Strecker reaction.^{26,27} Based on the mechanism of the catalytic enantioselective cyanosilylation of aldehydes using **6**, the Strecker reaction was proposed to proceed through a dual activation mechanism illustrated by intermediate **8**. These models (**7** and **8**) can explain the absolute configuration of the products.

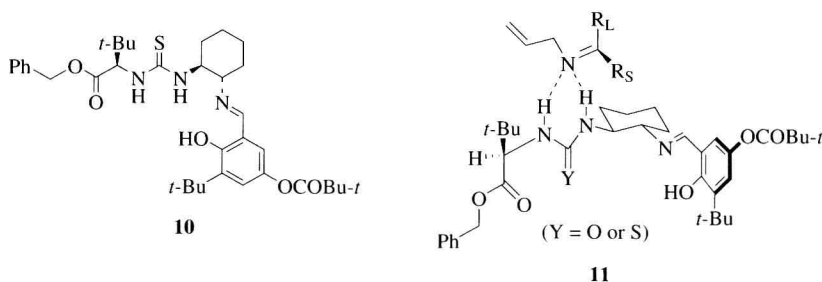


A dual activation mechanism illustrated by complex **9** was proposed for the catalytic enantioselective Strecker reaction of aldimines using a titanium–peptide complex.^{28,29} This transition state model was based on the mechanistic information obtained from kinetic studies, observation of a kinetic isotope effect, measurement of the activation enthalpy and entropy, and molecular modeling studies.³⁰ The titanium acts as a Lewis acid to activate the imines, while the terminal amide carbonyl oxygen acts as a Brønsted base to activate HCN, which is generated in situ from TMSCN and the additive *i*-PrOH. Specifically, the observed large negative entropy of activation ($\Delta S^\ddagger = -45.6 \pm 4.1 \text{ kcal/K}\cdot\text{mol}$) supports the notion that the reaction proceeds through the highly ordered transition state **9**.

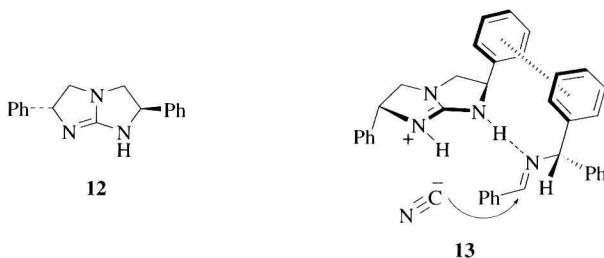


Chiral organocatalysts now provide an important class of reagents for asymmetric catalysis.³¹ Two significant asymmetric organocatalysts for the Strecker reaction have been reported, and both of these studies presented mechanistic proposals. One of the organocatalysts is the chiral thiourea catalyst **10**, which is one

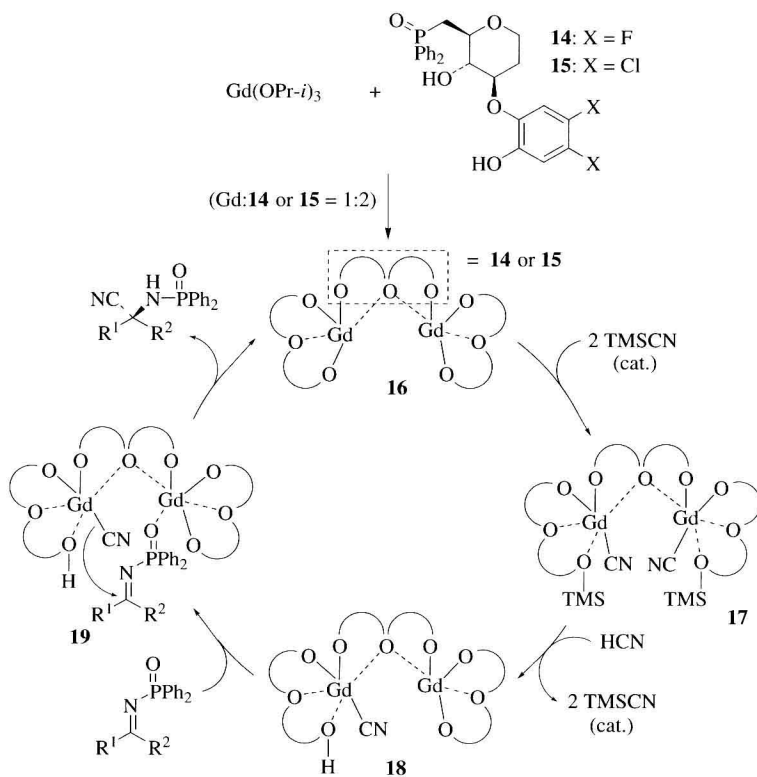
of the most useful asymmetric catalysts for the Strecker reaction of aldimines and ketimines.^{32–35} Detailed NMR and molecular modeling studies of the catalyst–imine complex demonstrated that the E- and Z-imine geometrical isomers of acyclic imines rapidly interconvert in the presence of the thiourea catalyst, and that the reaction proceeds from the Z-imine complexed to the thiourea moiety of the catalyst through hydrogen bonding as in **11** ($Y = S$).³⁶ In accord with this pre-transition-state model, a cyclic Z-imine (3,4-dihydroisoquinoline) is an excellent substrate for the Strecker reaction, producing the product in quantitative yield with 89% ee. The absolute stereoiduction from the cyclic Z-imine is identical to that of all of the Strecker adducts derived from acyclic imines that exist predominantly as E isomers. In addition, high-level calculations suggested that the catalyst binds to the starting imine more strongly than to the product; the energy of formation of the thiourea catalyst–imine complex is 10.0 Kcal/mol, while that of the catalyst–product complex is 6.3 Kcal/mol. Thus, product inhibition is unlikely to occur.



The other useful organocatalyst for the Strecker reaction is the chiral C-2-symmetric bicyclic guanidine catalyst **12**.³⁷ This catalyst was proposed to promote the Strecker reaction through a dual activation mechanism as shown in intermediate **13**. The nucleophile HCN is deprotonated by the basic guanidine, while the substrate imine undergoes hydrogen bonding to the protonated guanidine catalyst. A proximal phenyl group of the catalyst can undergo π -stacking with one of the benzhydryl phenyls of the imine. This well-organized pre-transition state model defines the approach of cyanide to the activated imines, and can explain the absolute configuration of the product.



Ketimines are generally much less reactive than aldimines. Therefore, an asymmetric catalyst with higher activity is required to promote the enantioselective Strecker reaction of ketimines. Chiral thiourea catalyst **10** can promote this type of reaction³⁸ through a similar mechanism to that shown in complex **11**. Chiral gadolinium catalyst **18** can promote the asymmetric Strecker reaction of *N*-diphenylphosphinoyl ketimines.^{39–41} The active catalyst was generated from $\text{Gd}(\text{OPr-}i)_3$ and D-glucose-derived chiral ligand **14** in a 1:2 ratio (Scheme 1). Protic additives such as 2,6-dimethylphenol or HCN dramatically accelerated the reaction, as well as improved the enantioselectivity. Based on ESI-MS studies, the active catalyst was proposed to be a 2:3 complex (**18**) of gadolinium and **14**, which was generated through reaction of initially formed alkoxide complex **16** with TMSCN giving compound **17**, followed by protonolysis. The Strecker reaction should proceed through an intramolecular transfer of a cyanide to the activated imine by the second Lewis acidic gadolinium (**19**). The proton in the asymmetric catalyst should accelerate the dissociation of the product from the catalyst (from **19** to **16**), and thus accelerate the catalytic cycle. Regeneration of the active catalyst **18** from **16** requires TMSCN . Direct conversion of **16**



Scheme 1