

Asymmetric Strecker Reactions

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1. INTRODUCTION

The well-known Strecker reaction was first documented by the German chemist Adolph Strecker (1822–1871) in 1850.¹ It was one of the earliest one-pot and atom economic multi-component reactions discovered. By a simple mixing of the easily available acetaldehyde, ammonia, and hydrogen cyanide for a fixed period of time, the resulting amino nitrile adduct was formed in high yield. Subsequent hydrolysis of the amino nitrile afforded alanine. Hence this facile synthesis led to the first amino acid to be synthesized in the laboratory even before its isolation from natural sources. Since this discovery, the Strecker reaction gradually attracted more and more attention from organic and biochemists. Even today after more than one and a half centuries, it remains very popular. This is largely because it provides a robust, direct, and economically viable access to various α -amino acids, both naturally and non-naturally occurring.² Besides serving as well-known α -amino acid precursors, after deprotonation α -amino nitriles also act as valuable and versatile equivalents of acyl anions. In addition, when they lose a cyanide anion under certain conditions, they act as iminium ion equivalents, which play important roles in the synthesis of natural products, heterocycles, and others.³ The use of an α -amino nitrile functioning as a C-protective group for a chiral α -amino aldehyde has also been reported.⁴

Spurred on by the ever-increasing demand for a range of enantioenriched α -amino acids for use in many fields^{2b,5} such as the life sciences,⁶ chemistry,⁷ and a range of industrial applications,⁸ one of the hottest topics in organic chemistry in recent years has been asymmetric Strecker reactions. Over the last four decades, enormous research effort has contributed to the considerable progress made in this area. In general two strategies have been used to achieve successful asymmetric Strecker reactions and optically active α -amino nitriles. The first is the nucleophilic addition of cyanide to chiral nonracemic imines. The second is the catalytic enantioselective cyanation of achiral imines.

With respect to the chiral nonracemic imines strategy for asymmetric Strecker reactions, the imine chiral moieties can originate from aldehydes or ketones, amines, or both. Although asymmetric Strecker reactions using chiral aldehyde- or ketone-derived imines can be found in many natural product syntheses of specific structures, this strategy tends to be extremely specific and highly structure-dependent. Hence, only those examples in which excellent chiral induction effects have been observed are used here to elucidate this particular strategy.^{9–31} In contrast, the use of chiral optically pure amines as the chiral auxiliary for

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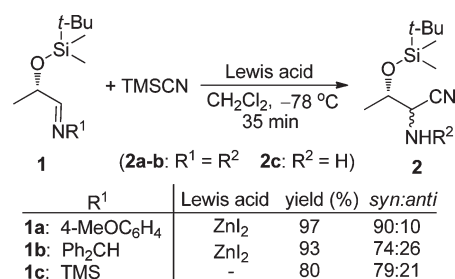
achieving the highly diastereoselective Strecker reaction has evolved into a relatively general and robust approach for accessing various enantiomerically pure α -amino acids. The performance of this strategic type of reaction requires stoichiometric amounts of chiral auxiliaries. After the reaction, the auxiliary groups must be cleaved from the products. In some cases, the chiral auxiliaries can be recovered and reused. The first example of such a chiral auxiliary-assisted Strecker reaction was reported by Harada in 1963,³² more than 110 years after the discovery of the Strecker reaction itself. Enantiopure (*S*)- α -phenylethylamine was used to replace the ammonia in the classic Strecker reaction. As a result of this modification, the corresponding α -amino nitrile was formed in a diastereoselective ratio of 3.3:1. After further transformations, the chiral alanine was obtained in an overall yield of 17% and with 90% ee. As a result of this important breakthrough, more and more optically active α -amino acids were successfully prepared in the same way.^{33–41} In addition, extensive studies involving other chiral amines which included α -amino acids,⁴² α -amino amides,⁴³ α -amino alcohols,^{44–51} sulfinamides,^{52–61} glycosyl amines,^{62–64} hydrazines,^{65–68} and others^{69–71} as the chiral auxiliaries were carried out sequentially. High yields and diastereoselectivities were achieved in many cases.

On the other hand, catalytic enantioselective Strecker reactions turn out to be another potential strategy for obtaining enantiomerically pure α -amino nitriles. In general, a prochiral substrate and only substoichiometric amounts of chiral catalyst were required. The key to this strategy is judicious choice of an efficient chiral catalyst needed to promote the given enantioselective Strecker reaction. Although this is a relatively new research field compared with the chiral auxiliary-assisted Strecker reaction, its development has been extremely fast since the first report of such a catalytic asymmetric Strecker reaction appeared in 1996.⁷² Further explosive achievements have been made during the last 15 years. Until now, various novel and efficient catalysts based on a range of catalytic models such as hydrogen bonding activation, Lewis base activation, and Lewis acid–Lewis base bifunctional activation have all been reported. In fact, catalytic enantioselective Strecker reactions have become the method-of-choice in the synthesis of chiral nonracemic amino nitriles.

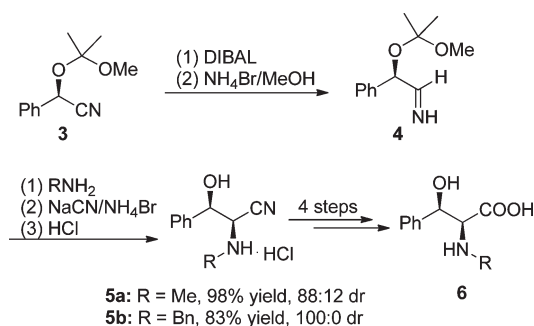
Together with the development of these asymmetric Strecker reactions, several timely reviews appeared that summarized and highlighted achievements in this field.⁷³ For example, Gröger comprehensively summarized the accomplishments achieved in the catalytic enantioselective Strecker reactions of aldimines and ketimines from 1996 to 2003.^{73b} The catalytic enantioselective cyanation of C=N bonds such as occurs in the Reissert reaction was also included. In addition, three reviews published by Yet,^{73a} Spino,^{73c} and Connon,^{73d} in which selected topics were briefly reviewed, appeared. Book chapters by North^{73e} in 2004 and Shibasaki^{73g} in 2008 concisely covered catalytic asymmetric Strecker reactions together with some representative experimental procedures for the synthesis of various chiral enantio-enriched α -amino nitriles. In 2009, Merino, Herrera and co-workers presented an overview of organocatalyzed Strecker reactions. Here reports of the enantioselective cyanation of imines and related compounds before 2009 were included and discussed.^{73e}

Since Gröger's review in 2003,^{73b} a number of great breakthroughs have been made in the field of asymmetric Strecker reactions, in particular the catalytic enantioselective method. Many structurally new chiral metal complexes and organic

Scheme 1. Asymmetric Strecker Reaction of Aldimines Derived from *O*-Protected (2*S*)-Lactic Aldehyde



Scheme 2. One-Pot Reduction–Transimination–Hydrocyanation Procedure To Transform Optically Active *O*-Protected Cyanohydrin to β -Hydroxy- α -cyanoamines



molecules were developed for use as highly efficient catalysts. Their use has led to excellent yields and enantioselectivities being achieved. Among the other attractive advances that have been made are the application of new cyanide sources, the use of imine equivalents as substrates, the exploration for more efficient catalysts for the three-component Strecker reaction, and the design of recyclable catalysts. It is pertinent therefore, that an updated overview of the asymmetric Strecker reaction with an emphasis on the work published after 2003 appears.

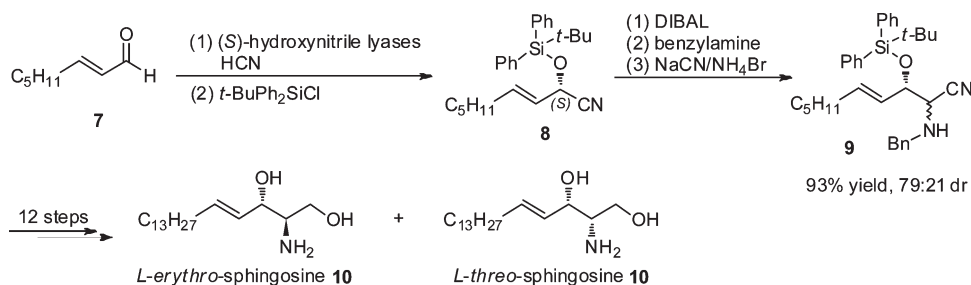
With the particular aim of giving a full view of the history and development of the asymmetric Strecker reaction, those reactions employing various kinds of chiral nonracemic imines will be summarized in this review. In addition, the asymmetric cyanation of some other classes of imine-like substrates including nitrones, iminium salts, and hydrazones will also be covered.

2. DIASTEREOSELECTIVE STRECKER REACTIONS OF CHIRAL NONRACEMIC IMINES AND ANALOGUES

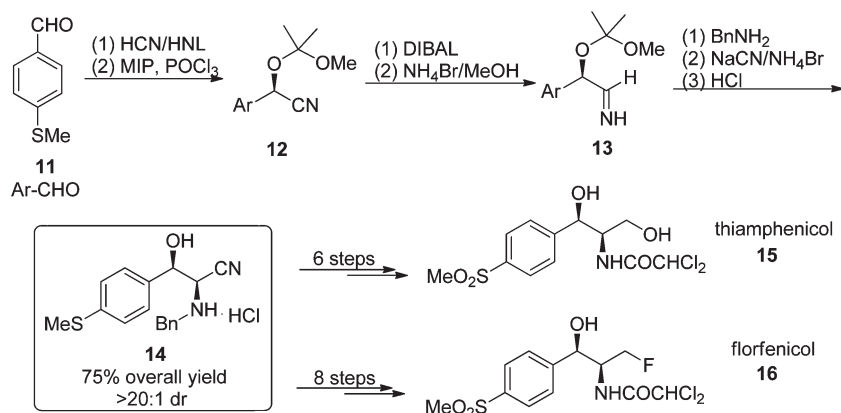
2.1. Chiral Nonracemic Imines as Substrates

Cainelli et al. reported the asymmetric Strecker reaction of *N*-substituted aldimines derived from the *O*-protected (2*S*)-lactic aldehydes.⁹ The optimal reaction conditions varied for the imines with different *N*-protected groups that were used (Scheme 1). Among the Lewis acids tested, ZnI₂ proved the most suitable for the imines 1a and 1b. Interestingly, the imine 1c (R¹ = TMS) was capable of reacting with trimethylsilyl cyanide (TMSCN) smoothly without a Lewis acid, affording the *N*-unprotected product 2c (R² = H) in good yield and with reasonable diastereoselectivity.

Scheme 3. Synthesis of L-Sphingosines



Scheme 4. Synthesis of Thiamphenicol and Florfenicol



In 1992, Brussee et al. reported a creative one-pot reduction–transimination–hydrocyanation procedure for the efficient transformation of the optically active *O*-2-methoxy-isopropyl (MIP)-protected mandelonitrile to yield the β -hydroxy- α -cyanoamines (Scheme 2).¹⁰ The diisobutylaluminum hydride (DIBAL) reduction of MIP-protected (*R*)-cyanohydrin 3 gave the primary imine 4. This was subsequently transformed into the more stable *N*-alkyl imine by a transimination reaction in the presence of methylamine or benzylamine. Hydrocyanation of the resulting secondary imines, followed by deprotection of the MIP group, afforded the β -hydroxy- α -cyanoamines 5 with good to excellent diastereoselectivities in favor of the (2*R*,3*R*) configuration. It should be noted that when the *N*-Bn imine was subjected to this one-pot hydrocyanation reaction, the *threo*-diastereoisomer was formed exclusively in high yield. This method has also been used in the synthesis of D- and L-sphingosines 10 (Scheme 3),¹¹ thiamphenicol 15, and florfenicol 16 (Scheme 4).¹²

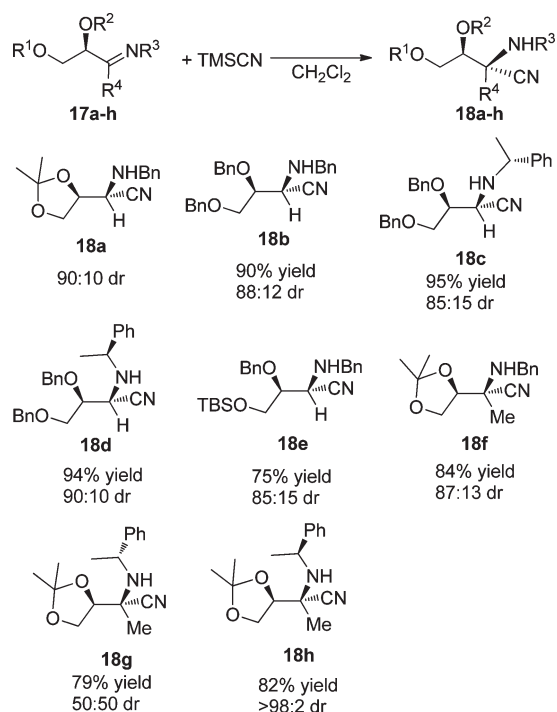
Cativiela and co-workers studied the diastereoselective Strecker reaction of chiral aldimines 17 derived from protected D-glyceraldehydes (Scheme 5).¹³ The best results were obtained when the reactions were carried out at room temperature in CH_2Cl_2 in the absence of a Lewis acid. High yields and good diastereoselectivities are reported. The reaction proved less stereoselective when Lewis acids were present. They also investigated the methyl ketone-derived counterparts.¹⁴ In a similar procedure, the product with the *R* configuration at the newly formed stereogenic center was predominantly formed at -20°C in CH_2Cl_2 . Interestingly, the effect of the reaction temperature on the diastereoselectivity was found to be solvent-dependent. When CH_2Cl_2 was used as the solvent for the asymmetric

cyanation of 17f, comparable yields and diastereoselectivities were found for temperatures ranging from -20°C to room temperature. In sharp contrast, when the reactions were performed in *i*-PrOH, the product *syn*-18f was preferentially obtained at -20°C by a kinetically controlled process. The *anti*-isomer, on the other hand, became the major product at room temperature through a thermodynamically controlled process. As expected, it was observed that both the diastereomerically pure *syn*-18f and *anti*-18f epimerized in *i*-PrOH to reach the same thermodynamic ratio (*syn/anti* = 34:66) after 2 days at room temperature. However, neither of them underwent epimerization in CH_2Cl_2 .

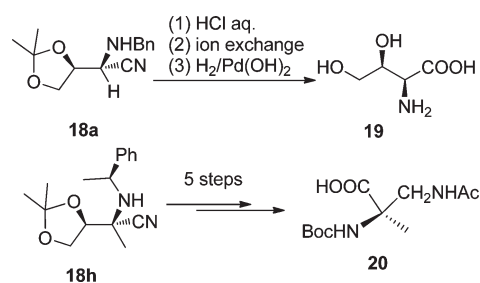
The double stereodifferentiation effect was also investigated by using enantiopure α -phenylethylamine (α -PEA) as the chiral auxiliary. Although little influence was observed for the aldehyde-derived imines (18c vs 18d), a great improvement was achieved for the methyl ketone-derived imines when the chirally matched α -PEA was employed (18g vs 18h). The *syn*-diastereomer 18h was formed almost exclusively (Scheme 5). In addition, the resulting optically active α -amino nitriles could be used to develop some useful chiral optically active compounds such as the (*R*)-(2-aminomethyl)alanine derivative 20 (Scheme 6).

In 1994, Reetz et al. reported the highly diastereoselective Strecker reaction of three classes of *N*-protected aldimines 21 derived from chiral *N,N*-dibenzylamino aldehydes, which could be prepared from the corresponding enantiopure α -amino acids.¹⁵ In the presence of a proper Lewis acid, various α , β -diamino nitriles 22 were synthesized with good yields and diastereomeric excesses (Table 1).

Scheme 5. Diastereoselective Strecker Reaction of Chiral Aldimines and Ketimines Derived from Protected D-Glyceraldehydes



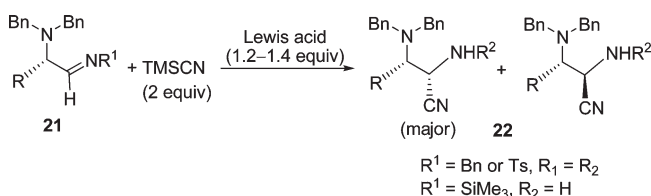
Scheme 6. Conversion of the Optically Active α -Amino Nitriles



Bernardi and co-workers developed a cyanobis(dibenzylamino)-borane-mediated transformation of various chiral aldehydes into the corresponding α -amino nitriles **25**.¹⁶ Those aldehydes bearing rigid frameworks at the α -position generally gave satisfying diastereoselectivities (Scheme 7).

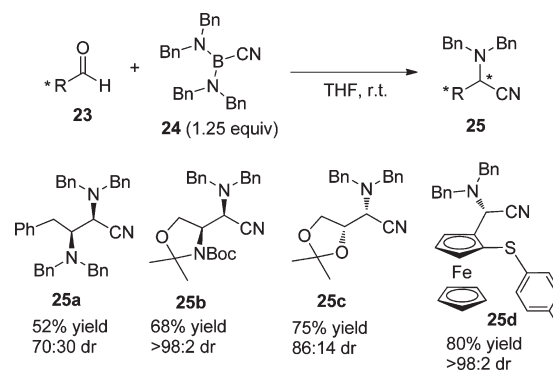
The Strecker reaction of the *N*-Bn-protected imine from the α -amino aldehyde **27** that in turn was derived from *L*-cysteine was used as a key step by Seki et al. for the asymmetric synthesis of (+)-biotin **30**.¹⁷ Two methods were developed to realize the Strecker reaction (Scheme 8). For method A, the amino aldehyde **27** was first treated with benzylamine, then with TMSCN in toluene, to give the desired chiral α -amino nitrile **28** in favor of a *syn*-configuration with high yield (96%) and diastereoselectivity (*syn/anti* = 28:1). They established the additional method B for the use of cheap cyanide reagents. The aldehyde **27** was first treated with aqueous sodium bisulfate to give the water-soluble sodium bisulfate adduct **29** quantitatively. After a simple workup, the aqueous solution could be

Table 1. Diastereoselective Strecker Reaction of Aldimines Derived from Chiral *N,N*-Dibenzylamino Aldehydes



| R | R ¹ | Lewis acid | solvent | T (°C) | yield (%) | dr |
|-----------------------------------|----------------|-----------------------------------|---------------------------------|------------|-----------|-------|
| Bn | Bn | TiCl ₄ | CH ₂ Cl ₂ | −78 to 20 | 81 | >95:5 |
| Bn | Bn | SnCl ₄ | Et ₂ O | −78 | 75 | 92:8 |
| Bn | Bn | BF ₃ ·OEt ₂ | CH ₂ Cl ₂ | −78 | 76 | 94:6 |
| Me ₂ CHCH ₂ | Bn | BF ₃ ·OEt ₂ | CH ₂ Cl ₂ | −78 | 22 | >95:5 |
| Me | Ts | BF ₃ ·OEt ₂ | CH ₂ Cl ₂ | −78 to rt | 49 | 90:10 |
| Bn | Ts | BF ₃ ·OEt ₂ | CH ₂ Cl ₂ | −78 to rt | 83 | 96:4 |
| <i>i</i> -Pr | Ts | BF ₃ ·OEt ₂ | CH ₂ Cl ₂ | −78 to rt | 53 | >95:5 |
| Me ₂ CHCH ₂ | Ts | BF ₃ ·OEt ₂ | CH ₂ Cl ₂ | −78 to rt | 59 | 92:8 |
| Me | TMS | Et ₂ AlCl | Et ₂ O | −40 | 72 | 93:7 |
| Bn | TMS | Et ₂ AlCl | Et ₂ O | −40 | 83 | 94:6 |
| Me ₂ CHCH ₂ | TMS | Et ₂ AlCl | Et ₂ O | −40 to −20 | 64 | 91:9 |

Scheme 7. Cyanobis(dibenzylamino)borane-Mediated Transformation of Chiral Aldehydes into α -Amino Nitriles



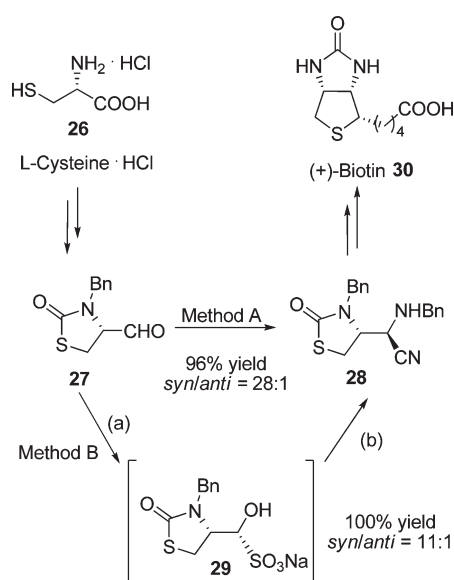
directly treated with benzylamine, followed by NaCN to provide the α -amino nitrile in quantitative yield and high diastereoselectivity (*syn/anti* = 11:1).

Alvarez-Ibarra et al. found that the α -sulfinylketimines **31a,b** could undergo asymmetric cyanide addition in the presence of Lewis acids (Table 2).¹⁸ The best results were achieved by using ZnCl_2 as the promoter and *i*-PrOH as the solvent. Subsequently, Martín Castro and co-workers reported other examples of the asymmetric cyanation reaction of imines using **31c–g** with a chiral sulfinyl moiety either with or without a Lewis acid catalyst.¹⁹ Moderate to good yields and diastereoselectivities were obtained. Interestingly, the β -sulfinylenamine **31'** also proved good substrate. It was assumed that in the presence of ZnCl_2 , the β -sulfinylenamine **31'** was transformed to the highly reactive iminium that was subsequently attacked by cyanide to afford the adduct **32h**.¹⁸

Using an asymmetric Strecker reaction as the key step, De Micheli et al. developed a stereoselective synthesis of the

conformationally constrained bicyclic α -amino acid **35** using the optically active bicyclic ketone **33**.²⁰ It should be noted that ZnCl_2 promoted the highly stereoselective asymmetric Strecker reaction of the corresponding *N*-4-methoxybenzyl (PMB)-protected ketimine.

Scheme 8. Stereoselective Strecker Reaction Used for the Synthesis of (+)-Biotin^a



^a Method A: (i) BnNH_2 (1.0 equiv), MgSO_4 , 5–25 °C, 3 h; (ii) TMSCN (2 equiv), toluene, 0–25 °C, 15 h. Method B: (a) NaHSO_3 (1.1 equiv), AcOEt , H_2O , 20 °C, 18 h; (b) (i) BnNH_2 (1.7 equiv), CH_2Cl_2 , 20 °C, 2 h; (ii) NaCN (1.2 equiv), 8–20 °C, 20 h; (iii) NaHSO_3 (0.3 equiv), NaCN (0.3 equiv), 20 °C, 1.5 h.

The only detectable stereoisomer was the α -amino nitrile **34**. Oxidative deprotection of the PMB group using an excess of cerium(IV) ammonium nitrate (CAN) followed by hydrolysis of the cyano group delivered the desired bicyclic α -amino acid **35** (Scheme 9).

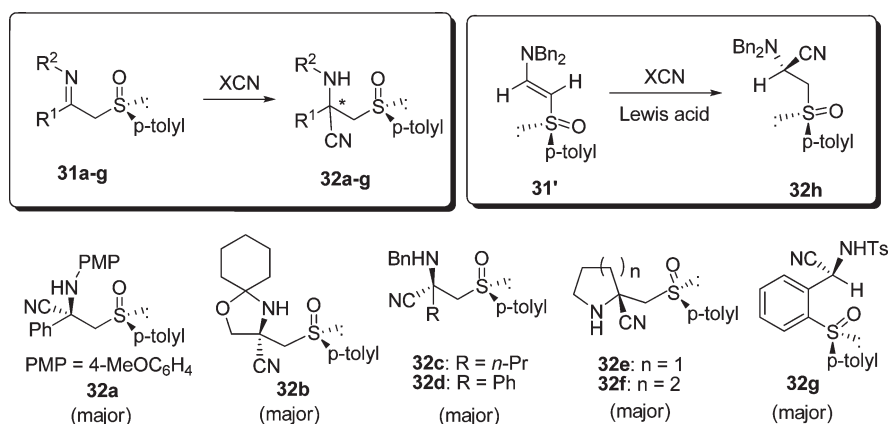
A Strecker reaction of the ketimine derived from the enantiopure bicyclic ketone **37** gave the α -amino nitrile **38** with high yield and diastereoselectivity (13.1:1 dr). This reaction was easily extended to give the corresponding enantiopure α -amino acid (+)-**39** in high yield (Scheme 10).²¹

Turner et al. described a highly enantioselective enzyme-catalyzed oxidative desymmetrization of substituted *meso*-pyrrolidines **40**.²² The monoamine oxidase MAO-N D5 variant was found to be the most suitable enzyme for this transformation. It provided a range of chiral Δ^1 pyrrolines with high enantioselectivities and good yields. Most importantly, when the resulting Δ^1 pyrrolines were employed as substrates in a Strecker reaction in CH_2Cl_2 at room temperature, using *in situ* generated HCN from TMSCN/MeOH as the cyanide reagent, the diastereoselectivities of the reactions were found to be very high (Scheme 11). Thus this method allowed facile access to a variety of highly optically pure 3,4-disubstituted proline analogues or bicyclic amino acids, which are crucial building blocks in medicinal research and drug development.

2.2. Chiral Nonracemic Nitrones as Substrates

To the best of our knowledge, the use of chiral nitrones as substrates in stereoselective Strecker-type reactions was first attempted by Merino et al. Various chiral α -hydroxyamino nitriles were prepared with good to high diastereoselectivities and yields (Table 3).²³ The study was initiated using the acyclic substrates **44a–h** derived from chiral compounds such as D-glyceraldehyde and L-serine. Several cyanide reagents such as

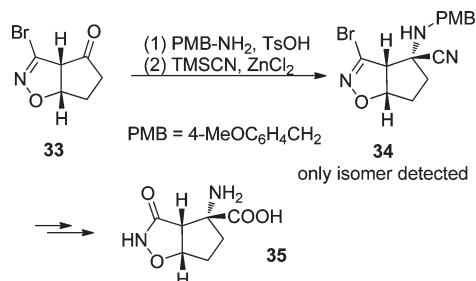
Table 2. Lewis Acid Catalyzed Asymmetric Cyanation of α -Sulfinylketimines and β -Sulfinylenamines



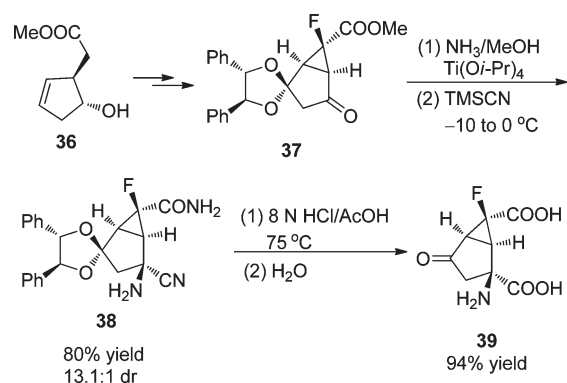
| XCN | Lewis acid | imine/XCN/LA | solvent | product | yield (%) | dr |
|--------------------------|-----------------|--------------|----------------|------------|-----------|-------|
| TMSCN | ZnCl_2 | 1/1/1 | <i>i</i> -PrOH | 32a | 60 | 86:14 |
| TMSCN | ZnCl_2 | 1/2.2/1 | <i>i</i> -PrOH | 32b | 28 | 72:28 |
| Et_2AlCN | | 1/2/0 | THF | 32c | 90 | 66:34 |
| Et_2AlCN | | 1/2/0 | THF | 32d | 50 | 88:12 |
| Et_2AlCN | CeCl_3 | 1/2/1.5 | THF | 32e | | |
| Et_2AlCN | CeCl_3 | 1/2/1.5 | THF | 32f | 95 | 75:25 |
| Et_2AlCN | | 1/2/0 | THF | 32g | 90 | 90:10 |
| TBDMSCN | ZnCl_2 | 1/1/2 | <i>i</i> -PrOH | 32h | 88 | 72:28 |

TMSCN, Et₂AlCN, Bu₄CN, and LiCN were investigated. TMSCN and Et₂AlCN turned out to be the best candidates. Et₂AlCN exhibited much higher reactivity than TMSCN, and this was attributed to its stronger acidity. The reaction of nitrones with TMSCN in CH₂Cl₂ gave *O*-TMS-protected α -hydroxyamino nitriles in good yields and diastereoselectivities. Subsequently these could be readily transformed into the corresponding α -hydroxyamino nitriles by treatment with citric acid/MeOH (4% p/v) at room temperature. α -Hydroxyamino nitriles could also be directly obtained using Strecker reactions in MeOH. In this case, the active cyanide

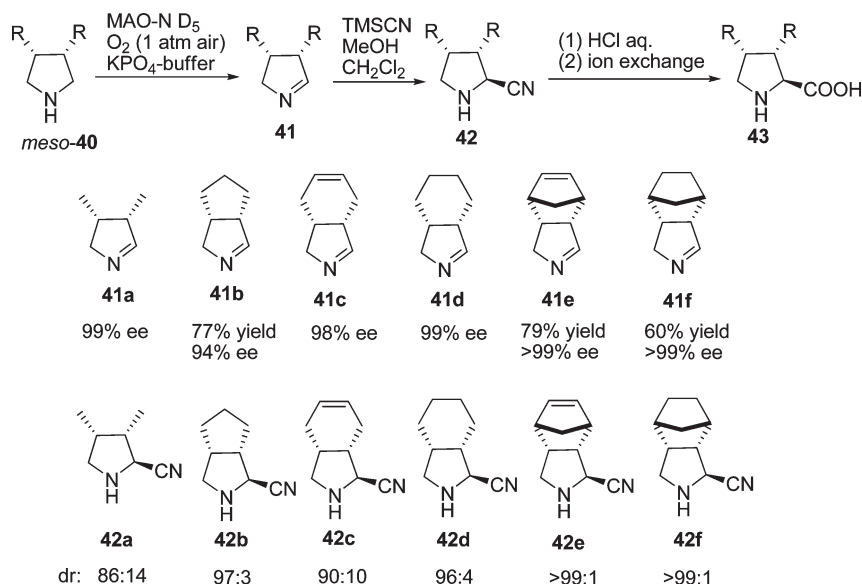
Scheme 9. Highly Stereoselective Strecker Reaction in the Synthesis of Cyclic α -Amino Acid



Scheme 10. Stereoselective Strecker Reaction in the Synthesis of Cyclic α -Amino Acid



Scheme 11. Highly Stereoselective Strecker Reaction of Chiral Δ^1 Pyrrolines



reagent is expected to be HCN produced from TMSCN and MeOH. In contrast, higher reactivity was observed by using Et₂AlCN as the cyanide reagent, and better diastereoselectivity was achieved when the reaction was carried out in THF and at a lower temperature (−60 °C).

Subsequently, Merino, Goti, and co-workers studied the stereoselective addition of TMSCN and Et₂AlCN to chiral cyclic nitrones **44i–n**.²⁴ Intriguingly, in all of the cases examined, complete stereoselectivities were observed for the asymmetric cyanation of chiral nitrones using TMSCN, the *trans*-isomer being exclusively formed. Moreover, the reaction was greatly sped up by using 0.2 equiv of a Lewis acid (Et₂AlCl or TMSOTf). The reaction time was dramatically shortened from 16 h to 5 min with the yield and stereoselectivity uninfluenced. However, although the yields remained excellent, only low to moderate diastereoselectivities (<9:1 dr) were observed when Et₂AlCN was used as the cyanating agent. The usefulness of this method was further demonstrated by the authors in the synthesis of a series of chiral optically active substituted 2-aminomethyl pyrrolidines **47** (Scheme 12). Interestingly, the absolute configuration of the newly formed stereogenic center C-2 in the cyano adduct of the cyclic nitrone **44i** could be efficiently inverted by an oxidation/reduction protocol. In addition, it proved possible to apply the same conversion to **44m** and **44n**. When the compounds **45i** and **46** were subjected to a Pd-catalyzed hydrogenation, the corresponding chiral 2-aminomethyl pyrrolidines (dihydrochloride salts) **47** were obtained in quantitative yields. By the same approach, α -hydroxyamino nitriles derived from the nitrones **44m** and **44n** were also transformed into the corresponding chiral substituted 2-aminomethyl pyrrolidines in excellent yields.

2.3. Chiral Nonracemic Iminium Salts as Substrates

Iminium salts are highly reactive species and are easily attacked by a variety of nucleophiles. It was reported by Scribner that the 17-keto steroid **48** reacted smoothly with pyrrolidine in the presence of 1 equiv of TsOH to give the iminium salt **49** in high yield (97%). This could subsequently react with sodium cyanide stereoselectively in acetonitrile to provide the 17- α -cyano steroid **50** in 85% yield (Scheme 13).²⁵

Table 3. Stereoselective Addition of Cyanide to Chiral Nonracemic Acyclic and Cyclic Nitrones

$$\begin{array}{ccc} \text{R}^3\text{-N}^+\text{=O}^- & \xrightarrow{\text{XCN}} & \text{R}^3\text{-N}^+\text{OR}^4 \\ | & & | \\ \text{R}^1 & & \text{R}^1 \\ | & & | \\ \text{R}^2 & & \text{R}^2\text{CN} \end{array}$$

44a-n R^1 or $\text{R}^2 = \text{H}$ **45a-n** $\text{R}^4 = \text{H}$ or TMS

44i: $\text{R} = t\text{-Bu}$
44j: $\text{R} = i\text{-Pr}_3\text{Si}$
44k: $\text{R} = \text{MOM}$ **44l** **44m** **44n**

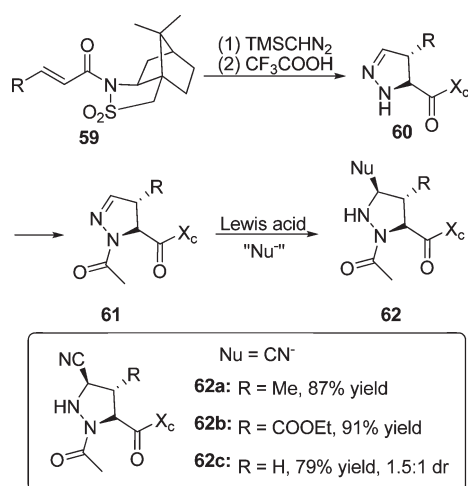
| nitrone | XCN (equiv) | solvent | T (°C) | time (h) | <i>syn/anti</i> | yield (%) | R ⁴ |
|--------------------------|----------------------------|---------------------------------|--------|----------|--------------------|-----------|----------------|
| | TMSCN (5.0) | CH ₂ Cl ₂ | 0 | 48 | >95:5 | 84 | TMS |
| | Et ₂ AlCN (1.1) | THF | 0 | 6 | 86:14 | 91 | H |
| | TMSCN (3.0) | MeOH | 0 | 48 | 83:17 | 100 | H |
| | Et ₂ AlCN (1.1) | THF | −60 | 6 | 90:10 | 95 | H |
| | TMSCN (3.0) | MeOH | 0 | 48 | 92:8 | 100 | H |
| | Et ₂ AlCN (1.1) | THF | −60 | 6 | 90:10 | 86 | H |
| | TMSCN (3.0) | MeOH | 0 | 48 | 70:30 | 96 | H |
| | Et ₂ AlCN (1.1) | THF | −60 | 6 | 65:35 | 90 | H |
| | TMSCN (3.0) | MeOH | 0 | 48 | >95:5 | 100 | H |
| | Et ₂ AlCN (1.1) | THF | −60 | 6 | >95:5 | 96 | H |
| | TMSCN (3.0) | MeOH | 20 | 48 | 71:29 | 100 | H |
| | Et ₂ AlCN (1.1) | THF | −40 | 6 | 73:27 | 100 | H |
| | TMSCN (3.0) | CH ₂ Cl ₂ | 0 | 48 | 68:32 | 94 | TMS |
| | Et ₂ AlCN (1.1) | THF | −40 | 6 | 75:25 | 90 | H |
| | TMSCN (3.0) | MeOH | 0 | 48 | 70:30 | 100 | H |
| | Et ₂ AlCN (1.1) | THF | −60 | 6 | 76:24 | 96 | H |
| 44i-n | TMSCN (1.0) | CH ₂ Cl ₂ | 25 | 16 | <1:20 ^b | 100 | TMS |
| 44i-m^a | TMSCN (1.0) | CH ₂ Cl ₂ | 25 | 5 min | <1:20 ^b | 100 | TMS |

^a TMSOTf or Et₂AlCl (0.2 equiv) was added. ^b The ratio of *cis/trans*.

Santamaria et al. reported the photocyanation of the tertiary amines **51** involving the *in situ* generated iminium salts **52** as the key intermediates.²⁶ Several structurally complex tertiary amines were stereoselectively transformed

into the corresponding α-amino nitriles **53** in high yields (Scheme 14).

Another example of a highly stereoselective cyanide addition to the iminium salts is shown in Scheme 15. In the presence of

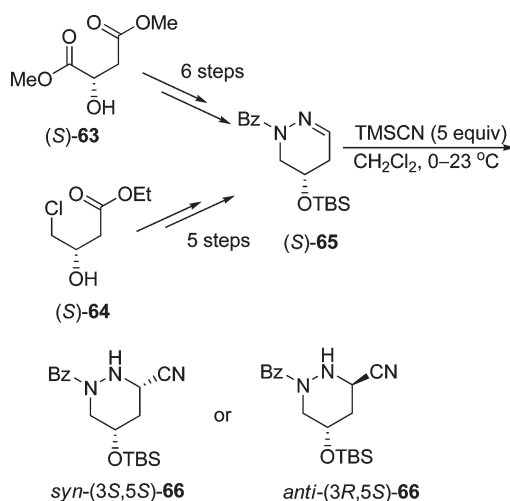
Scheme 17. Diastereoselective Addition of TMSCHN₂ to Chiral Nonracemic *N*-Acyl Pyrazolines

For instance, although the cyanation of 4-substituted substrates such as **61a,b** gave rise to only a single diastereomer, as determined by ¹H NMR analysis, the reaction employing the substrate **61c** without a substituent on the 4-position led to the product with only extremely low diastereoselectivity.

Optically pure 5-hydroxypiperazic acids (HOPip) with various configurations at the stereogenic centers have been shown to be essential building blocks for some kinds of cyclodepsipeptides bearing strong anticancer activity. Among the efforts to stereoselectively synthesize 5-hydroxypiperazic acids, Hamada and co-workers established an efficient protocol to achieve this class of rare amino acids. A diastereoselective Strecker-type reaction of the enantiopure cyclic hydrazone **65** promoted by Lewis acids was used as the key step.³⁰ The compound **65** was prepared either from the commercially available chiral nonracemic malic acid ester **63** or the 4-chloro-3-hydroxybutanoic acid ester **64**. After extensive screening of potential Lewis acid catalysts, the authors found that a diastereoselectivity of 81:19 in favor of the *syn* isomer could be obtained by using 1 equiv of Zn(OTf)₂ as the catalyst and 1 equiv of AcOH together with 0.1 equiv of NaOAc as the additives. Interestingly, by employing 0.05 equiv of Mg(OAc)₂ as the catalyst and 1 equiv of HOAc as the additive, the diastereoselectivity of the reaction could be totally reversed. In this case, reaction provided the desired amino nitrile in 99% yield and 3:97 dr but with the *anti* isomer as the predominant product (Scheme 18). By virtue of this fact, anyone of the four diastereomers could be prepared as the predominant isomer as needed by judicious choice of a suitable chiral substrate and catalyst system. In addition, further purification to yield the diastereopure product was facile since the *anti* and *syn* isomers could be easily separated using silica gel column chromatography. It was assumed that the Strecker reaction proceeds under kinetic control because no epimerization was observed when the diastereopure product was subjected to the same reaction conditions in the presence of a Lewis acid and additives. The corresponding *N*-Boc-protected esters **69** were prepared with moderate yields (51–59%) by transforming the resulting amino nitriles **66** via three steps (Scheme 19).

Using Hamada's synthetic route and starting from the (*R*)-4-chloro-3-hydroxybutanoic acid ester **64**, Lindsley et al. described a modified protocol that took advantage of a microwave-assisted organic synthesis.³¹ As a result of using the microwave technique,

Scheme 18. Diastereoselective Strecker-type Reaction of Enantiopure Cyclic Hydrazone



the reaction time was greatly shortened for four of the reaction steps. The overall yield of the methyl ester **68** was also improved. Although it was found that Hamada's procedure was unsuitable for the preparation of the intermediate *N*-Boc-protected ester **69** on a large scale, the alternative intermediates, the *N*-Alloc protected esters **71** and **73**, were successfully prepared for the purpose of the total synthesis of piperazimycin A (Scheme 19).

3. ASYMMETRIC STRECKER REACTION ASSISTED BY CHIRAL AUXILIARY

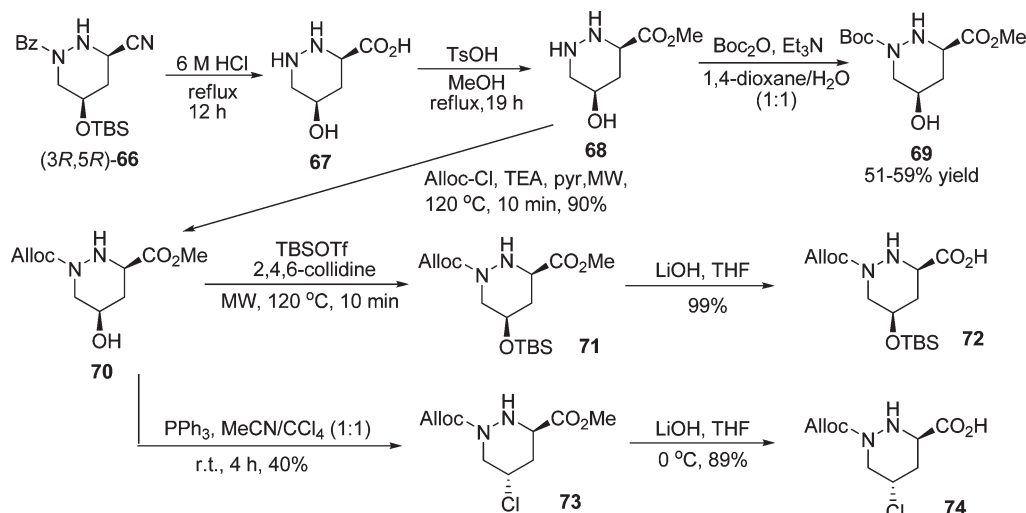
3.1. α -Phenylethylamine as the Chiral Auxiliary

More than 110 years after Strecker's seminal report in 1850, the first asymmetric Strecker reaction was achieved by Harada in 1963 using (*S*)- α -phenylethylamine **75** (α -PEA) as the chiral auxiliary.³² His method involved the reaction of acetaldehyde, (*S*)-PEA, and hydrogen cyanide to afford the α -amino nitrile **76**, the hydrolysis of which (using 5 N HCl) gave the corresponding *N*-alkyl amino acid hydrochloric salt **77**. Removal of the methylbenzyl group by Pd-catalyzed hydrogenolysis delivered the desired alanine **78** in 17% overall yield with 90% ee (Scheme 20). Subsequent study indicated that the high optical purity of the alanine was due to the fractional crystallization operation used in the procedure. In actual fact, the diastereoselectivity of the cyanide addition step was only 3.3:1 dr.^{33,34}

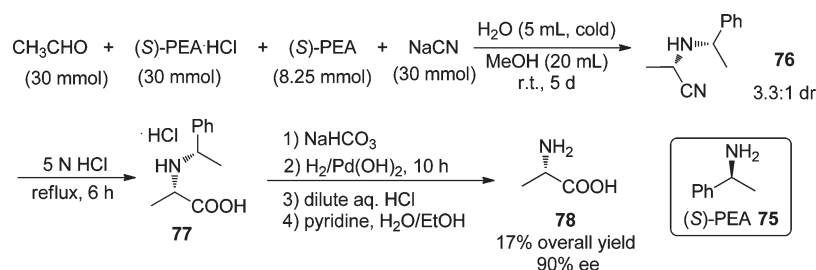
In 1983, Stout et al. described a detailed study of the diastereomeric synthesis of various amino nitriles from aromatic or aliphatic aldehydes, sodium cyanide, and enantiopure PEA at room temperature.³³ The diastereomeric ratio was generally found to be around 3.0:1. Through repeated crystallization of the hydrochloride salts of the products, various optically pure diastereomers were obtained in low to moderate yields.

By using a CN-modified hemin copolymer as the cyanide reagent for reaction with chiral aldimines derived from enantiopure amines and aliphatic aldehydes, Harada and co-workers found that the diastereoselectivities for the cyanide addition step and overall yields of the α -amino acid were greatly improved.³⁴ In addition, two analogous chiral amines (*R*)-**79** and **80**, albeit with bulkier steric hindrance, were also examined as chiral inducers. They were found to give better diastereoselectivities (Table 4).

Scheme 19. Transformation of the Adduct to 5-Hydroxypiperazic Acid and Its Derivatives



Scheme 20. The First Asymmetric Strecker Reaction and Its Application in the Synthesis of Enantioenriched Alanine



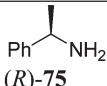
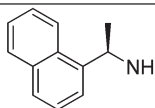
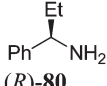
Saidi et al.³⁵ reported a diastereoselective Strecker reaction of the aldehyde, the chiral amine (*R*)-75 with TMSCN in the absence of catalysts under solvent-free conditions at room temperature. Various categories of aldehydes including aromatic, heteroaromatic, α,β -unsaturated, and aliphatic aldehydes were examined; high yields and moderate diastereoselectivities were obtained (68:32–86:14 dr).

Interestingly, the thermodynamically controlled 1,3-asymmetric induction of chiral α -amino nitriles derived from aldehydes and optically pure α -alkylbenzylamines was studied by Ogura et al.³⁶ The experiment was performed by dissolving the previously isolated diastereomerically pure α -amino nitriles (*R,R*)-81 and (*R,S*)-81 separately in MeOH, and then heating each of the solutions at 80 °C in sealed tubes for 3 h to complete the equilibration. The diastereomeric ratio at equilibrium was found to be as high as 90:10 when (*R*)- α -(*t*-Bu)-benzylamine was used as the chiral inducer. It was observed that the bulkiness of the substituent (*R*¹) of the chiral amine was crucial for achieving the high equilibrium dr ratio. On the other hand that of aldehyde (*R*²) had little effect (Scheme 21).

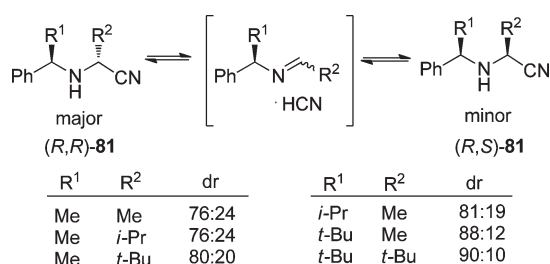
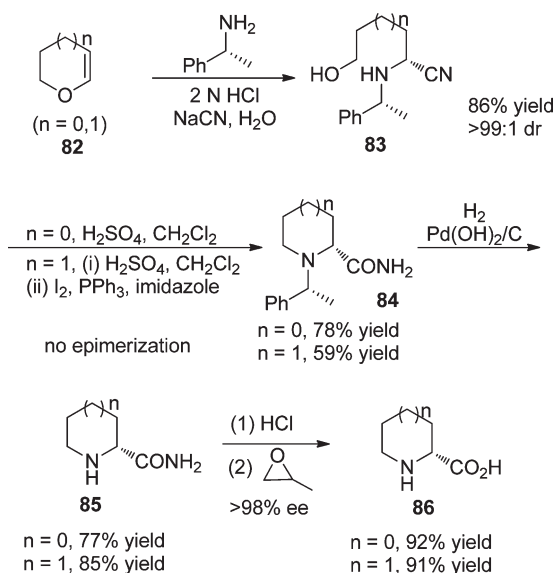
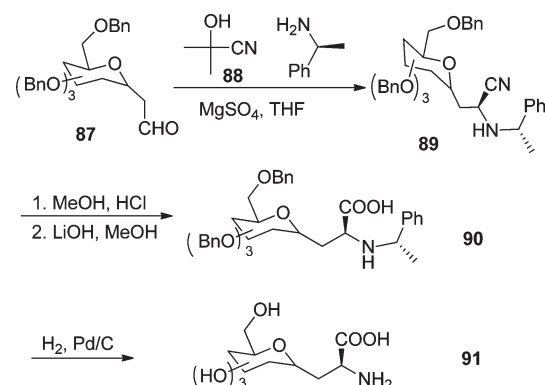
Using chiral PEA as the chiral inducer, the Fadel group³⁷ discovered an excellent method for accessing the enantiopure heterocyclic α -amino acids 86. This included pipecolic acid and proline synthesized from dihydropyran and dihydrofuran in 42% and 47.5% overall yields, respectively, via four steps. It should be noted that the diastereoselectivities exhibited in the cyanation step were extremely high (Scheme 22).

In 2000, Wong et al.³⁸ reported an asymmetric Strecker reaction for the successful synthesis of the biologically important

Table 4. CN-Modified Hemin Copolymer as the Cyanide Reagent

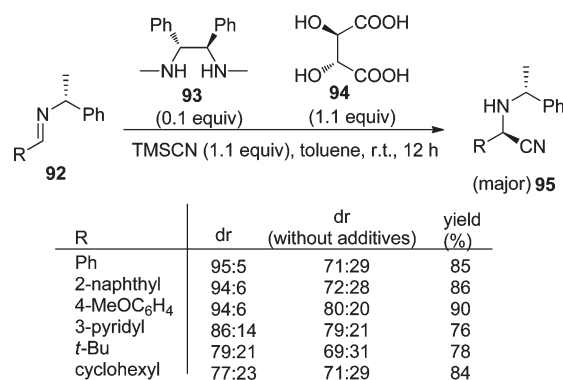
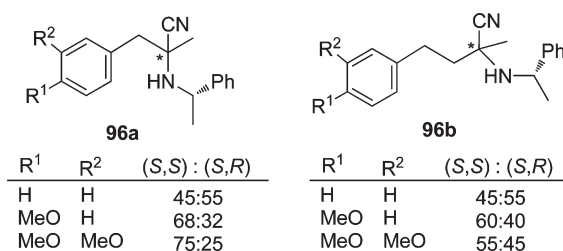
| chiral amine | aldehyde | product | yield (%) | dr |
|---------------------------------------------------------------------------------------------------------|-----------------|------------------|-----------|-------|
|  (<i>R</i>)-75 | MeCHO | (<i>S</i>)-Ala | 59 | 87:13 |
| | EtCHO | (<i>S</i>)-But | 53 | 88:12 |
| | BnCHO | (<i>S</i>)-Phe | 44 | 93:7 |
| | <i>i</i> -PrCHO | (<i>S</i>)-Val | 32 | 94:6 |
|  (<i>R</i>)-79 | MeCHO | (<i>S</i>)-Ala | 50 | 90:10 |
| | EtCHO | (<i>S</i>)-But | 44 | 91:9 |
| | BnCHO | (<i>S</i>)-Phe | 42 | 95:5 |
| | <i>i</i> -PrCHO | (<i>S</i>)-Val | 36 | 98:2 |
|  (<i>R</i>)-80 | MeCHO | (<i>S</i>)-Ala | 57 | 96:4 |
| | EtCHO | (<i>S</i>)-But | 46 | 98:2 |
| | BnCHO | (<i>S</i>)-Phe | 41 | >99:1 |
| | <i>i</i> -PrCHO | (<i>S</i>)-Val | 34 | 95:5 |

glycoalanine 91. They used (*S*)-PEA as the chiral inducer and achieved a good yield and diastereoselectivity (Scheme 23). Interestingly, although the sugar moiety was found to have no chiral induction effect for this reaction, based on the fact that no diastereoselectivity was observed when BnNH₂ was used instead of (*S*)-PEA in the selected cases, the diastereoselectivity varied greatly when imines with different sugar moieties were used. Another interesting phenomenon was that the diastereoselectivity of

Scheme 21. Thermodynamically Controlled 1,3-Asymmetric Induction of Chiral α -Amino Nitriles**Scheme 22. Synthesis of Cyclic α -Amino Acids with (*R*)-PEA as the Chiral Auxiliary****Scheme 23. Synthesis of C-Glycoalanine with (*S*)-PEA as the Chiral Inducer**

the cyanation step was solvent-dependent. Reversed stereoinduction was observed in some cases by changing the solvent from THF to CH_2Cl_2 .

In general, only moderate diastereoselectivity was obtained when enantiopure PEA was used as the chiral inducer. Hence, recrystallization or chromatographic separation was usually

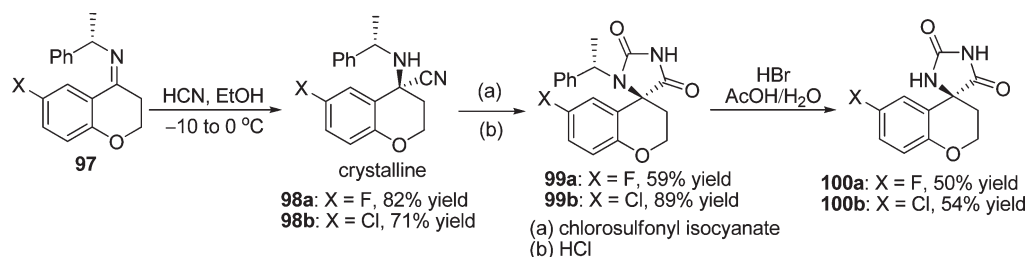
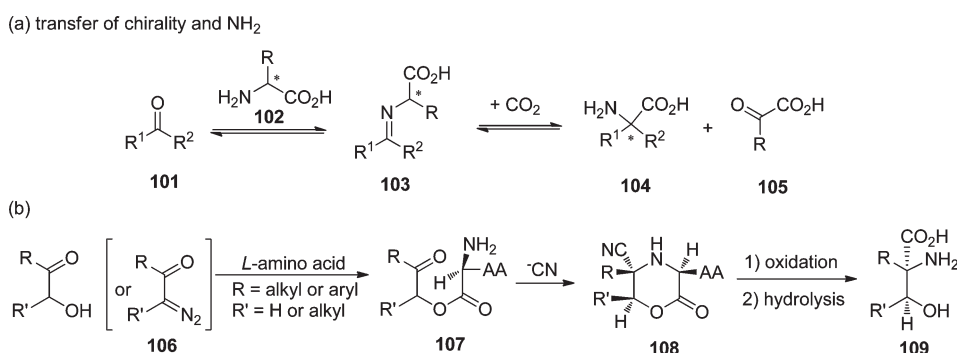
Scheme 24. Enhanced Diastereoselectivity by Addition of Chiral Diamine and Tartaric Acid**Scheme 25. Asymmetric Strecker Reaction of Arylalkyl Methyl Ketimines Derived from (*S*)-PEA**

needed to afford the enantiopure diastereomer. Interestingly, Mangeney et al.³⁹ found that the diastereoselectivity could be generally enhanced by the addition of chiral diamine **93** and tartaric acid **94** to the reaction mixture (Scheme 24). A preliminary mechanistic study indicated that the minor diastereomer formed exclusively in the early stages of the reaction. However, its formation virtually ceased later on, and the major product was overwhelmingly produced. This phenomenon was not observed in the reaction in the absence of the chiral additives. The authors assumed that autocatalysis might be occurring in this system and that the minor diastereomer might be promoting the formation of the major one.

In 1977, in addition to the asymmetric cyanation of imines derived from aldehydes and chiral PEA, Weinges et al.⁴⁰ examined the reaction of arylalkyl methyl ketimines to afford the α -amino nitriles **96** with a quaternary carbon chiral center. As shown in Scheme 25, the stereoselectivities were strongly related to the substituents on the aryl ring of the substrates.

Asymmetric Strecker reactions of the chiral ketimines **97** derived from cyclic ketones and enantiopure PEA were also tested by Sarges and co-workers (Scheme 26).⁴¹ Interestingly, the products, which were obtained in high yields, were determined by NMR to be diastereomerically pure. It was assumed that the HCN addition was reversible, and the precipitation of the less soluble diastereomer might be the driving force pushing the reaction toward the exclusive formation of the less soluble diastereomer. Another possibility was that the hydrocyanation step might be highly diastereoselective and that the minor diastereomer remained in the solution during the crystallization process. The diastereomerically pure chiral α -amino nitriles **98** were further reacted to give the biologically important optically active spirohydantoin **100** in three steps.

Scheme 26. Asymmetric Strecker Reaction of Chiral Cyclic Ketimines and (S)-PEA

Scheme 27. Synthesis of β -Hydroxy α -Amino Acid with α -Amino Acid as the Chiral Auxiliary

3.2. α -Amino Acid as the Chiral Auxiliary

Using one chiral α -amino acid to synthesize another α -amino acid sounds particularly interesting. It was speculated that such a reaction, which might involve an asymmetric transfer of the amino group from the α -amino acid **102** to the ketone **101** to produce a new α -amino acid **104**, might in fact occur in nature. The amino acid reactant **102** could be converted to the corresponding pyruvate derivative **105** (Scheme 27a). Inspired by this hypothetical biosynthetic route, Ohfuné and Shinada et al.⁴² designed a highly efficient protocol to access the β -hydroxy α , α -disubstituted α -amino acid **109**. This synthesis consisted of the following sequence of transformations: (1) synthesis of the α -acyloxy ketone **107** from a suitable ketone **106** and α -amino acid; (2) formation of a cyclic ketimine intermediate from α -acyloxy ketone by an intramolecular condensation; (3) stereoselective addition of cyanide to 1,4-oxazine to give the α -amino nitrile **108**; (4) oxidative conversion into the α -imino nitrile; and (5) removal of the chirality-transferring amino acid as a pyruvate derivative and hydrolysis of the nitrile group under acidic conditions to give the β -hydroxy α , α -disubstituted α -amino acid **109** (Scheme 27b). By this strategy, various α -substituted serines, threonines, and their acyclic or cyclic analogs in optically pure form were successfully synthesized.

3.3. α -Amino Acid Derived Amide as the Chiral Auxiliary

Broxterman and de Lange et al.⁴³ reported a diastereoselective Strecker reaction that employed the (*R*)-phenylglycine amide **110** as the chiral auxiliary. The Strecker reaction was accompanied by an *in situ* crystallization-induced asymmetric transformation, whereby one diastereomer selectively precipitated. The reaction was performed by the addition of NaCN/AcOH to (*R*)-phenylglycine amide **110** and pivaldehyde **111** in H₂O at 23–28 °C. The mixture was then heated to 70 °C and stirred for 24 h. After being cooled to 30 °C, the precipitated amino nitrile

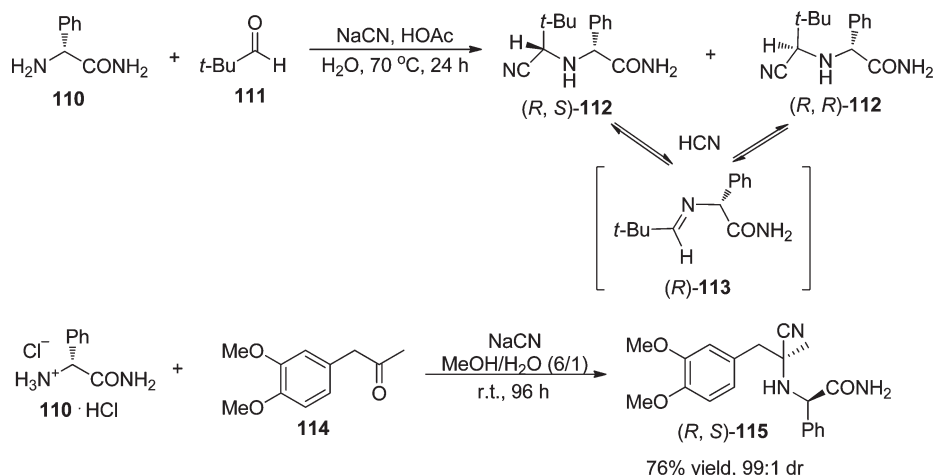
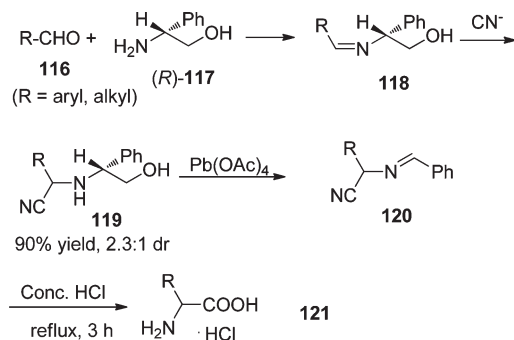
was filtered. As a result, the amino nitrile (*R,S*)-**112** was obtained in 93% yield and more than 99:1 dr. This phenomenal result could be explained as shown in Scheme 28. Apparently, at elevated temperatures, the diastereomeric outcome and yield of the process is controlled by the difference in the rates of the reversible conversions of the amino nitriles **112** to the intermediate imine **113**, as well as in the solubility of both diastereomers under the reaction conditions. However, at lower temperatures, the epimerization reactions were slower, and this led to lower diastereoselectivities. The diastereomerically pure α -amino nitrile (*R,S*)-**112** was successfully transformed in three steps into (*S*)-*tert*-leucine with a yield of 73% and an ee of >98%. Also, 3,4-dimethoxyphenylacetone **114** could also be employed as a substrate, giving the product **115** with 76% yield and 99:1 dr.

3.4. α -Phenylglycinol as the Chiral Auxiliary

α -Phenylglycinol **117** is another efficient auxiliary for asymmetric Strecker reactions. It can be easily prepared from the corresponding amino acid by reduction. After chiral induction, the *N*-protecting group was easily cleaved by oxidation with lead tetraacetate under mild conditions. Compared with the structure of chiral PEA, the additional hydroxyl group attached to **117** appears to play a unique role in the Strecker reaction.^{44–50}

Chakraborty et al.⁴⁴ and Hosangadi et al.⁴⁵ reported the diastereoselective Strecker reaction using optically pure phenylglycinol as the chiral inducer. They obtained good yields and diastereoselectivities (generally around 90% yield and 85:15 dr) for various aromatic and aliphatic aldehydes (Scheme 29).

In 2008, Liu et al.⁴⁶ developed an efficient method for the synthesis of β , β -difluoroamino acids with chiral phenylglycinol as the chiral inducer. The procedure consisted of six steps: Coupling the aryl iodides **122** with ethyl bromodifluoroacetate **123** gave the corresponding coupling products **124**, which were

Scheme 28. Diastereoselective Strecker Reaction with (*R*)-Phenylglycine Amide as the Chiral AuxiliaryScheme 29. α -Phenylglycinol as the Auxiliary for the Asymmetric Strecker Reaction

then transformed into the 2-difluoromethyl-1,3-oxazolidines **126** in two steps. Boron trifluoride etherate promoted the Strecker reaction of the 2-difluoromethyl-1,3-oxazolidines **126** to give the α -amino nitriles **127** in good yields (85–93%) and diastereoselectivities (90:10–98:2 dr). Removal of the chiral auxiliary and hydrolysis of the nitrile group afforded the β,β -difluorophenylalanine **128a** with 73% ee (partial racemization occurred during the hydrolysis of nitrile group) (Scheme 30).

Furthermore, with chiral phenylglycinol as the auxiliary, enantiopure α,α -disubstituted α -amino acids were synthesized starting from aryl alkyl ketones by the Ma group in 1999.⁴⁷ For example, heating a mixture of the ketone **131a** with (*R*)-phenylglycinol resulted in a mixture of the imine **132** and the 1,3-dioxazolidine **133**. Treatment of this mixture with TMSCN followed by transformation of the nitrile to the ester gave the corresponding *N*-protected amino ester **134** with a diastereoselectivity of 2:1. The diastereomer (*R,S*)-**134** was the major product. In addition, the (*R,S*)- and (*R,R*)-isomers could be separated by conversion to their *N*-Cbz derivatives **135**. By taking advantage of this methodology, four antagonists of metabotropic glutamate receptors **129–130**, (*S*)- α M4CPG, (*S*)-MPPG, (*S*)-AIDA, and (*S*)-APICA, were synthesized (Scheme 31).

In 2001, Warmuth et al.⁴⁸ reported a similar strategy for the synthesis of some other benzocycloalkane-1-amino-1-carboxylic acids by the addition of TMSCN to chiral phenylglycinol derived ketimines. The cyanide addition step showed that the

diastereoselectivities ranged from 1:2.9 to 1:25. Moreover, the diastereoselectivity was found to be both temperature- and solvent-dependent.

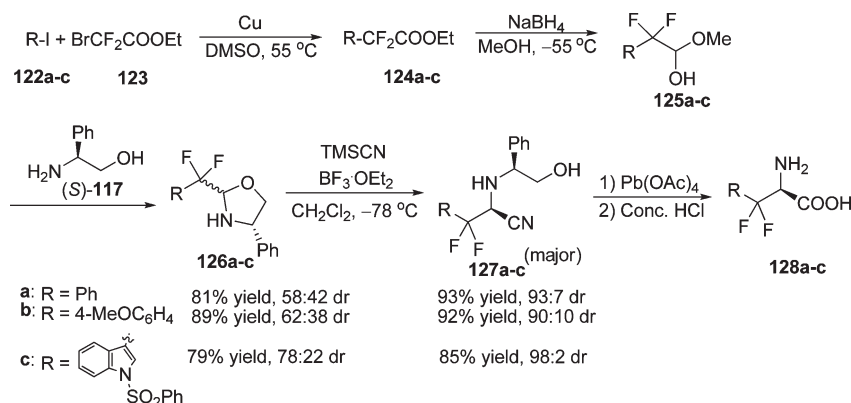
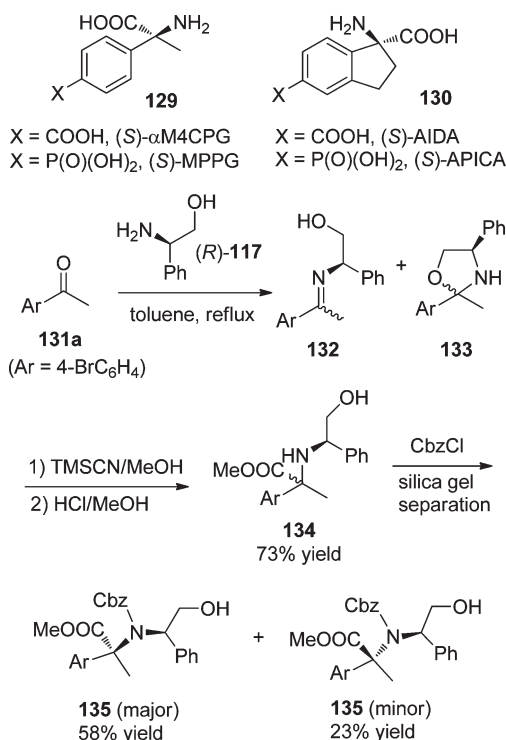
In 2004, the Ma group⁴⁹ developed a practical method for the synthesis of α -substituted or α,γ -disubstituted glutamic acids **142** using the asymmetric Strecker reaction of γ -ketoacids **136** induced by (*S*)-phenylglycinol (Scheme 32). Their synthetic procedures involved (1) the diastereoselective Strecker reaction of imines generated from γ -ketoacid sodium salts and (*S*)-phenylglycinol, (2) treatment of the resultant α -amino nitriles with HCl/MeOH and heating at 200 °C to give the bicyclic lactones **139** and **140**, and (3) hydrolysis and subsequent debenzoylation of **139** or their alkylation products **141** to furnish the desired α -substituted or α,γ -disubstituted glutamic acids **142**.

In 2006, using (*R*)-phenylglycinol as the chiral auxiliary, Brigaud et al.⁵⁰ successfully developed an efficient route for the synthesis of both enantiomers of α -trifluoromethyl alanine and various enantiopure diamines and amino alcohols with trifluoromethyl α -amino nitriles **144** as the key intermediates (Scheme 33). Although the diastereoselectivity of the Strecker-type reaction was moderate, the efficiency of the chromatographic separation of each α -amino nitrile diastereomer allowed convenient access to the enantiopure compounds.

Besides the (*R*)-phenylglycinol **117**, the Kobayashi group also tried (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol **147** as a chiral auxiliary in the asymmetric Strecker reaction.⁵¹ In the presence of 20 mol % of Yb(OTf)₃ and 100 mol % of 2,6-di-*t*-butyl-4-methylpyridine (DTMP), the three-component reaction of the aldehyde, **147**, and TMSCN proceeded smoothly to afford the desired product **148** in good yield and diastereoselectivity (Scheme 34).

3.5. Sulfonamide as the Chiral Auxiliary

The first asymmetric Strecker reaction to synthesize α -amino acids using enantiopure sulfinimines **149** was documented by Davis et al. in 1994.⁵² The reaction was performed with diethylaluminum cyanide (Et₂AlCN) as the cyanide reagent. It gave good yields (62–78%) and moderate diastereoselectivities (up to 83:17 dr). The reaction using other cyanide sources such as KCN and CuCN gave either no product or low yields. The major diastereomeric amino nitriles **150**, easily separated by silica

Scheme 30. Synthesis of β,β -Difluoroamino Acids with Chiral Phenylglycinol as the Chiral InducerScheme 31. Synthesis of Enantiopure α,α -Disubstituted α -Amino Acids with Chiral Phenylglycinol as the Auxiliary

gel chromatography on treatment with 3–6 N HCl, underwent deprotection of the *N*-sulfinyl group and hydrolysis of the nitrile at the same time to give the corresponding amino acids **121** or **151** without racemization. Two years later, an improved protocol was published by the same group using *i*-PrOH as the additive (Scheme 35).⁵³ The diastereoselectivity of the cyanide addition steps were generally enhanced to about 93:7 dr for aldimines. Since the release of ethane was observed, *i*-PrOH was assumed to react with Et₂AlCN to generate a more selective cyanide donor, namely, Et(*i*-PrO)AlCN. A possible transition state was proposed. In this, the aluminum coordinated with the sulfinyl oxygen of the sulfinimine to form a tetracoordinated species; then stereospecific intramolecular transfer of cyanide through a six-membered chairlike transition state afforded the adduct. Following this achievement, a series of related reports were published by

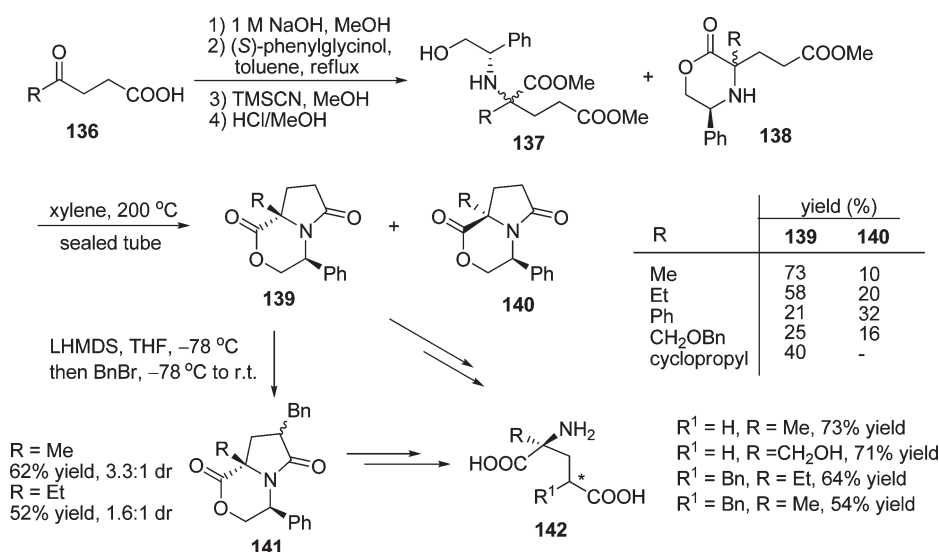
the Davis group. They extended the methodology to the asymmetric synthesis of other kinds of chiral amino acids bearing diverse substituted moieties or functional groups such as methyl, fluoride, and (*tert*-butyldimethylsilyl)oxyl.⁵⁴ It should be noted that for α,α -disubstituted sulfinimines with a chiral center in the α -position, the sulfinyl group played a predominant role on the asymmetric induction. Besides aldimines, ketosulfinimines were also investigated in detail under the same conditions. They gave products with up to 95% yield and 99:1 dr.⁵⁵

Although Davis et al.⁵² found that the reaction of TMSCN with a chiral imine derived from benzaldehyde and *p*-toluenesulfonamide gave none of the desired product or only low yields in the presence of a Lewis acid or base such as CsF, later studies by both the Cordi⁵⁶ and the Hou groups⁵⁷ showed that the enolizable sulfinimines could be successfully employed as the substrates for reaction with TMSCN under suitable conditions. For example, in the presence of 0.2 equiv of Sm(Oi-Pr)₃, the imine **149d** reacted efficiently with TMSCN at room temperature to give the product **150d** in 70% yield and 86:14 dr after 4 h (Scheme 36).⁵⁶ In addition, promoted by 1.05 equiv of CsF, various enolizable sulfinimines **149** were smoothly converted to the corresponding amino nitriles **150** in excellent yields and high diastereoselectivities (Scheme 37).⁵⁷ Moreover, good results for 2-aziridinesulfinimines and ketimines prepared from acetophenones and sulfonamide, respectively, were also obtained by the Hou group.

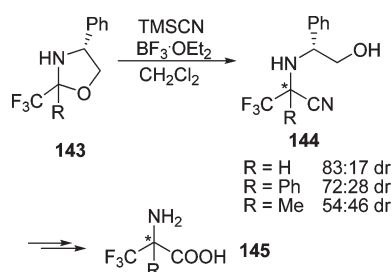
In 2005, Mukaiyama et al.⁵⁸ reported another case of a Lewis base-catalyzed diastereoselective Strecker reaction of TMSCN and the chiral sulfinimines **149** generated from (*S*)-*p*-toluenesulfonamide and aliphatic aldehydes. In the presence of 10 mol % of tetra-*n*-butylammonium acetate, the reaction proceeded smoothly in DMF/THF (2:1) to afford the corresponding α -amino nitriles **150** in high yields and good diastereoselectivities (Scheme 38). The compounds **150** with (*R,S*)-configurations were the major products.

Besides the extensively studied enantiopure *p*-toluenesulfonamide, chiral *tert*-butylsulfonamide has also been successfully applied as the chiral inducer in asymmetric Strecker reactions.⁵⁹ For example, Lu and co-workers⁶⁰ reported a solvent-controlled asymmetric Strecker reaction of **152** in the absence of a catalyst. This provides a convenient approach to various enantioenriched α -trifluoromethyl α -amino acids. When the chiral ketimine **152** and TMSCN were mixed in hexane at room temperature for 12–48 h, the adduct **153** was obtained in up to 92% yield and a 99:1 dr. However, the opposite asymmetric induction was

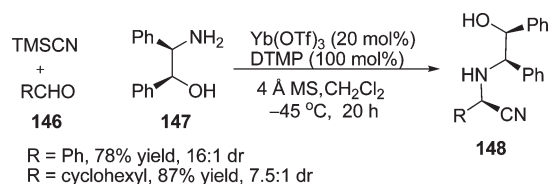
Scheme 32. Synthesis of α -Substituted and α,γ -Disubstituted Glutamic Acids through Asymmetric Strecker Reaction of γ -Ketoacids Induced by (*S*)-Phenylglycinol



Scheme 33. Synthesis of Optically Active Trifluoromethyl α -Amino Nitriles Using (*R*)-Phenylglycinol as the Auxiliary

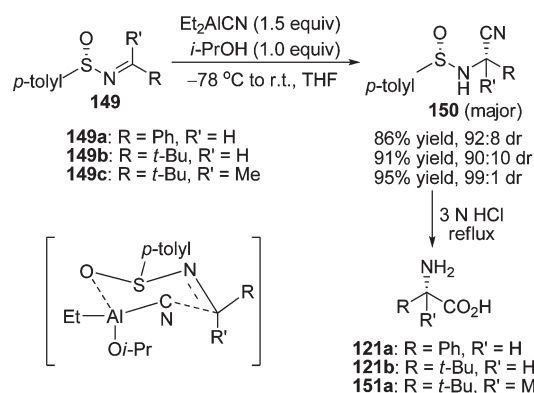


Scheme 34. Asymmetric Strecker Reaction with 147 as the Chiral Auxiliary

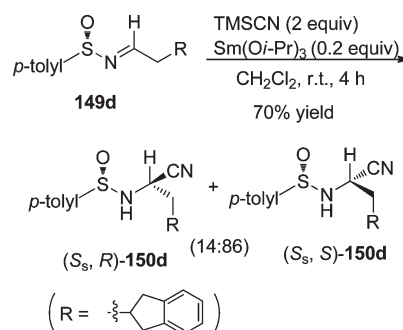


observed when DMF was used as the reaction medium. In this case the yield was up to 89% with a 1:19 dr (Scheme 39). It should be noted that the cyanation of sulfinimines without CF₃ did not react under similar conditions. The proposed mechanism to explain the solvent-controlled diastereoselectivity is shown in Scheme 40. In hexane, it was assumed that TMSCN was activated by the sulfinyl oxygen. **TS1** was disfavored because of the predominant electrostatic repulsion between the lone pairs on the sulfur and the electron-rich CF₃ group. Whereas in the case of DMF as the solvent, TMSCN was supposedly activated by the solvent. Hence **TS3** was more favorable because of the fact it has less stereoelectronic repulsion.

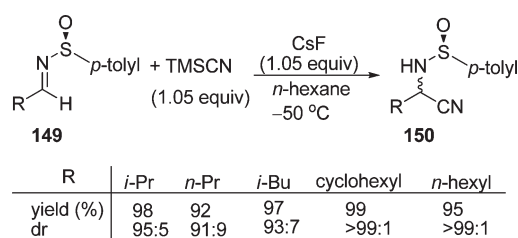
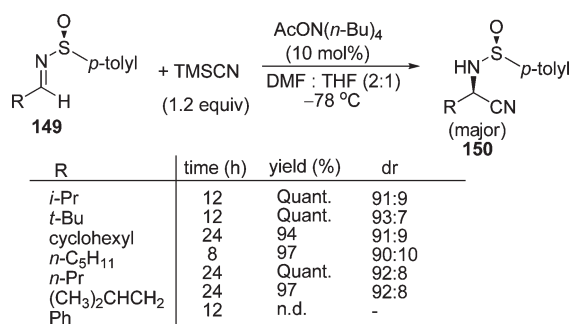
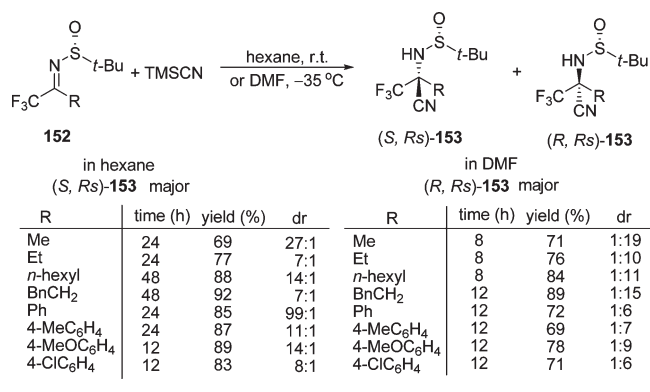
Scheme 35. Synthesis of α -Amino Acids Using Enantiopure Sulfinimine as the Chiral Inducer



Scheme 36. Sm(O*i*-Pr)₃-Catalyzed Asymmetric Strecker Reaction of Enolizable Sulfinimine

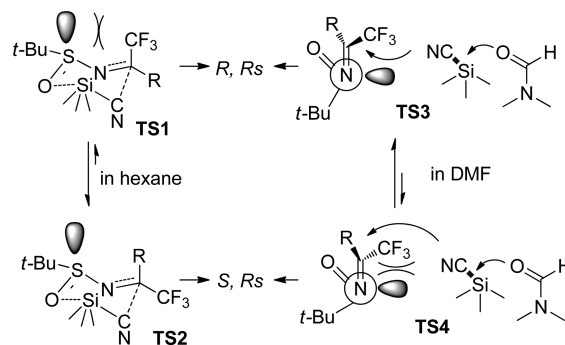
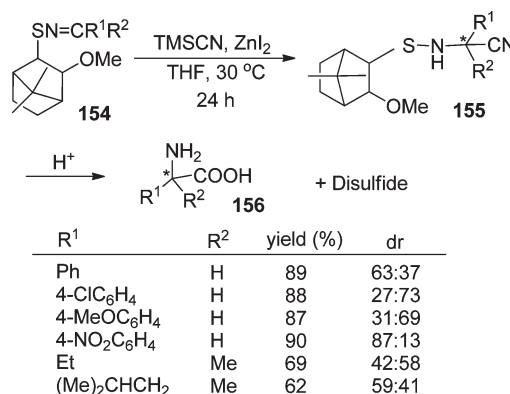


Mabic and Cordi⁵⁶ also made a detailed study of chiral *t*-butylsulfinimine, derived from 2-indanyl acetaldehyde, in a Strecker reaction. Using the Et₂AlCN/*i*-PrOH system established by Davis et al.,⁵² their reaction took place with a high yield

Scheme 37. CsF-Promoted Asymmetric Strecker Reaction of Enolizable Sulfinimines**Scheme 38. Tetra-*n*-butylammonium Acetate Catalyzed Diastereoselective Strecker Reaction of Chiral Sulfinimines and TMSCN****Scheme 39. Asymmetric Strecker Reaction Using Chiral *tert*-Butylsulfinamide as the Chiral Inducer**

(95%) and diastereoselectivity (97:3 dr) at room temperature in THF. Moreover, in the presence of a Lewis acid (20 mol %), TMSCN could also be used as an efficient cyanide donor. The best result was achieved by using Y(OTf)₃ as the catalyst; the product yield was 90% with 98:2 dr after reacting for 24 h at room temperature.

Additionally, in 1996 Jiang et al.⁶¹ investigated the chiral sulfinimines **154**, derived in turn from the (+)-camphors, as potential substrates for the asymmetric Strecker reaction. In the presence of 2 mol % of ZnI₂, good yields and moderate diastereoselectivities were obtained for the aldimines. Two examples of the corresponding chiral ketimines were also reported. However, only poor diastereoselectivities were reported (Scheme 41). The α -sulfinamino nitriles **155** were converted to the free α -amino acids **156** by treating with concentrated HCl.

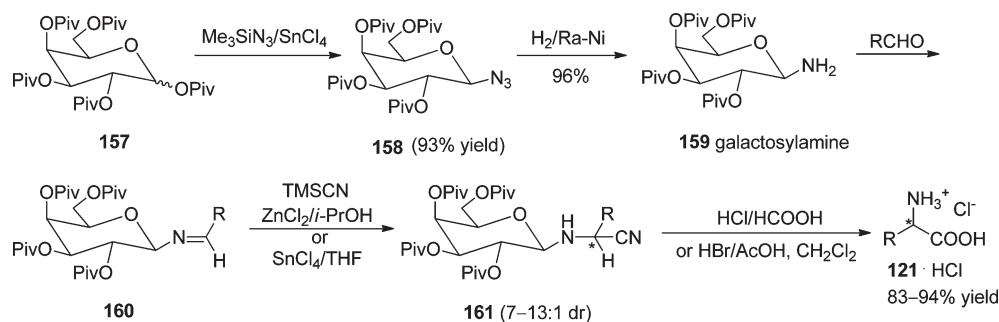
Scheme 40. Proposed Mechanism**Scheme 41. Asymmetric Strecker Reaction of Chiral Sulfinimines Derived from (+)-Camphor**

3.6. Glycosyl Amine as the Chiral Auxiliary

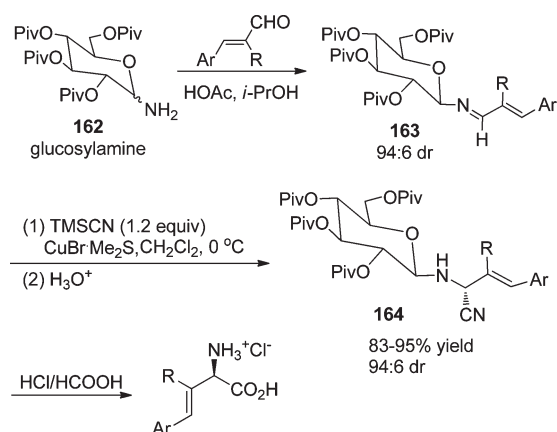
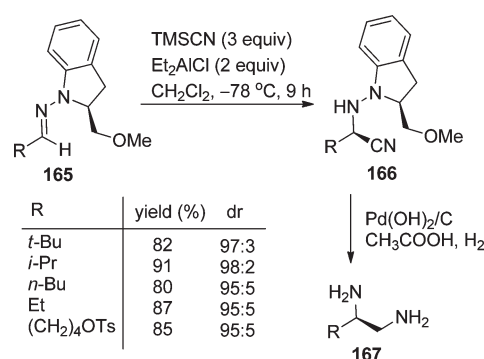
In 1987, Kunz et al.⁶² developed an asymmetric Strecker reaction using galactosylamine **159** as the efficient chiral auxiliary. It was easily prepared from penta-*O*-pivaloyl- β -D-galactopyranose **157** in two steps. The initial investigation of the three-component reaction of galactosylamine, aldehyde, and NaCN at room temperature showed that the desired products **161** could be obtained in almost quantitative yield and 3:1 to 7:1 dr. However, the reaction proceeded very slowly (2–4 weeks) and anomerization was observed. Subsequent studies⁶³ revealed a far superior modified process, in which the *N*-galactosylimines prepared from the galactosylamine and the corresponding aldehydes were treated with TMSCN in the presence of the Lewis acid (ZnCl₂ or SnCl₄). This gave the amino nitriles **161** in high yields and improved diastereoselectivities (7:1–13:1 dr). In the presence of an equimolar amount of catalyst, the reaction was completed within a few minutes at room temperature. Interestingly, while *R*-diastereomers were obtained in *i*-PrOH or THF, the *S*-diastereomers were obtained as the major products when CHCl₃ was used as the solvent and ZnCl₂ as the catalyst (Scheme 42).

Inspired by the above work, the Zhang group⁶⁴ reported the asymmetric Strecker reaction using the glucosylamine **162** as the chiral auxiliary. A series of amino acids including phenylglycine and β,γ -unsaturated amino acids were obtained with high yields and enantiopurities (Scheme 43).

Scheme 42. Asymmetric Strecker Reaction with Glycosylamine as the Chiral Auxiliary



Scheme 43. Asymmetric Strecker Reaction Using Glucosylamine as the Chiral Auxiliary

Scheme 44. Asymmetric Strecker Reaction with the Chiral Hydrazine (*S*)-1-Amino-2-Methoxymethylindoline

3.7. Hydrazine as the Chiral Auxiliary

In 1996, (*S*)-1-amino-2-methoxymethylindoline (SAMI) was successfully used by Kim and co-workers as an efficient chiral auxiliary in the asymmetric Strecker reaction to afford various highly diastereopure aliphatic α -hydrazino nitriles **166** (Scheme 44).⁶⁵ It is the first example of a diastereoselective addition of cyanide to chiral hydrazones. To establish the optimal reaction conditions, several solvents as well as a range of Lewis acids such as SnCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, and ZnCl_2 were investigated. The case where the hydrazone was prepared from pivaldehyde and SAMI was used as the model substrate. The best result (82% yield, 97:3 dr) was achieved when the reaction was promoted by 2 equiv of Et_2AlCl at -78°C in CH_2Cl_2 . Under the same conditions, several other aliphatic aldehyde-derived hydrazones also gave satisfactory results. The substrate with a moderately steric group *R* such as *i*-Pr gave a better yield and diastereoselectivity. It should be noted that cleavage of the N–N bond and reduction of the cyano group in the α -hydrazino nitriles **166** could be achieved in one-pot and at the same time by using $\text{Pd}(\text{OH})_2/\text{C}$ catalyst in acetic acid under H_2 to afford the optically active vicinal diamines **167**.

In 2003, the Enders group⁶⁶ reported another example of an asymmetric Strecker reaction using chiral hydrazine as the chiral inducer. In the presence of TiCl_4 (2.0 equiv) and Et_2O (4.2 equiv), the diastereoselective addition of TMSCN to (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP)-derived hydrazones **168** proceeded smoothly in CH_2Cl_2 to give the α -hydrazino nitriles **169** in high yields and diastereoselectivities (Scheme 45). The N–N bonds

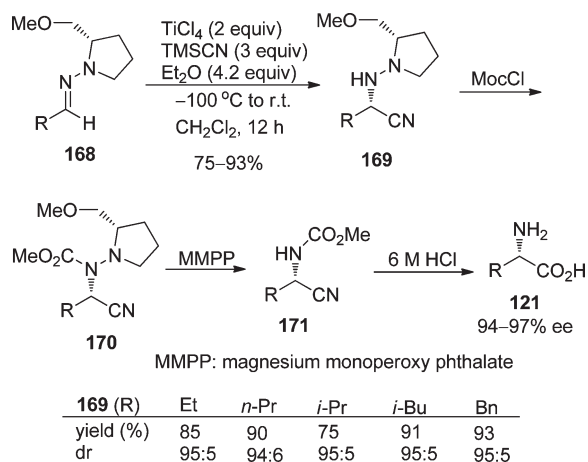
of the α -hydrazino nitriles were cleaved in an oxidative reaction, and the resulting α -amino nitriles **171** were then converted by acidic hydrolysis into the α -amino acids **121** with high ee values.

In 2006, Friestad and co-workers⁶⁷ described the addition of TMSCN to chiral oxazolidinone-derived *N*-acylhydrazones **172**. The diastereoselectivity was highly dependent on the substituent on the oxazolidinone moiety, and the 4-phenyl-2-oxazolidinone was found to display the best stereocontrol. The reactions gave good yields and modest diastereoselectivities for aliphatic hydrazones but only moderate yields albeit with excellent diastereoselectivities for the aromatic compounds (Scheme 46).

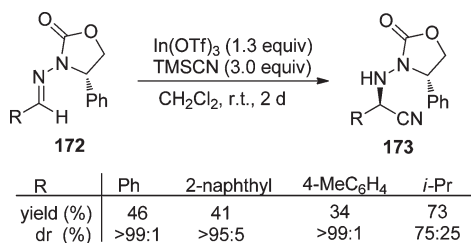
Fernández et al. revealed in 2008 that (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine could also act as an excellent chiral auxiliary for asymmetric Strecker reactions.⁶⁸ In the presence of 1.0 equiv of Et_2AlCl at -78°C , cyanosilylation of the chiral hydrazones **174**, derived from aliphatic aldehydes and (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine, generally gave excellent conversions and diastereoselectivities (91:9–99:1 dr) (Scheme 47). Moreover, the pure major diastereomer could be isolated in high yield (80–84%) by column chromatography. A reasonable explanation for the observed configuration of the major diastereomer obtained was given based on computational calculations.

Besides the above-mentioned chiral amine auxiliaries, some other special chiral amine auxiliaries such as (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane⁶⁹ and (–)-carvone-derived chiral α -amino nitriles⁷⁰ were developed for use in asymmetric Strecker reactions. Moderate to good diastereoselectivities were obtained. In addition, optically pure PEA and phenylglycinol were successfully applied to the asymmetric synthesis of chiral cyclic quaternary amino acids with two or

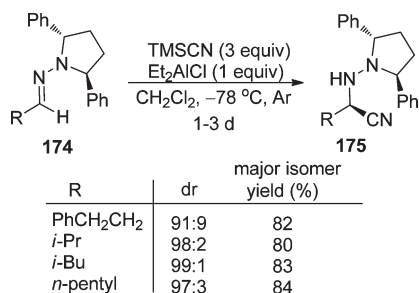
Scheme 45. Asymmetric Strecker Reaction with the Chiral Hydrazine (S)-1-amino-2-methoxymethyl-pyrrolidine as the Chiral Inducer



Scheme 46. Asymmetric Strecker Reaction of Chiral Oxazolidinone-Derived *N*-Acylhydrazones



Scheme 47. Asymmetric Strecker Reaction with (2*S*,5*S*)-1-Amino-2,5-Diphenylpyrrolidine as the Chiral Auxiliary

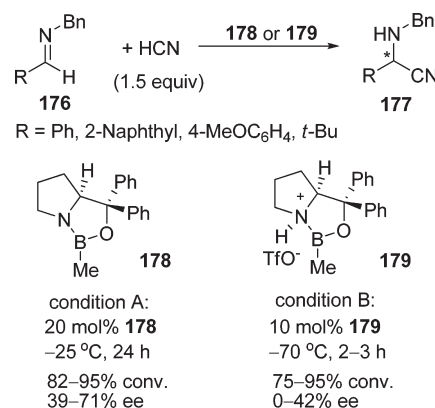


more chiral centers. These have been well summarized and discussed in an excellent recent review.⁷¹

4. CATALYTIC ENANTIOSELECTIVE STRECKER REACTION

In 1996, the Lipton group⁷² reported the first example of a catalytic enantioselective Strecker reaction. Catalyzed by 2 mol % of a cyclic dipeptide, the asymmetric addition of HCN to *N*-benzhydryl imines proceeded smoothly to give the desired products in excellent yields and ee values. Since then, the catalytic enantioselective Strecker reaction has attracted more and more attention, and a number of highly efficient catalyst systems have been developed.

Scheme 48. Oxazaborolidine- and Protonated Oxazaborolidine-Catalyzed Enantioselective Strecker Reaction of *N*-Bn Aldimines



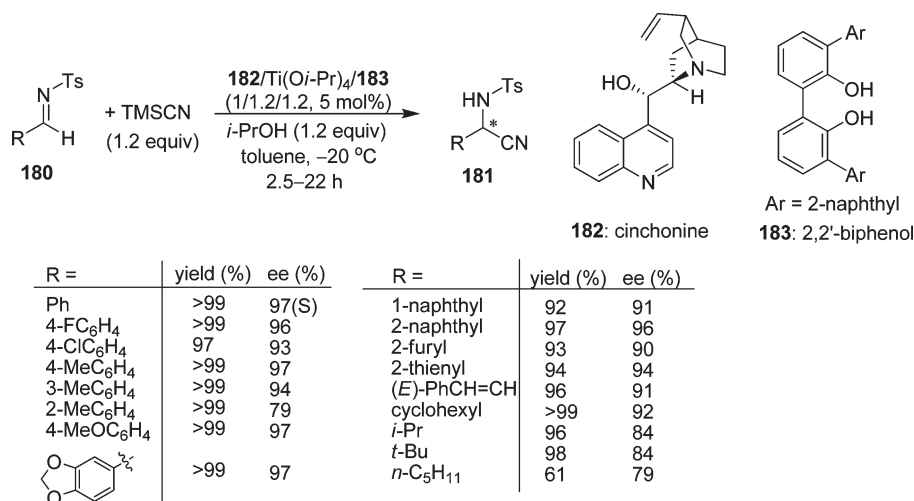
This section is divided into three parts: (1) catalytic enantioselective Strecker reactions using aldimine as the substrate; (2) catalytic enantioselective Strecker reactions using ketimine as the substrate; (3) catalytic enantioselective Strecker reactions using imine equivalents as the substrate. The former two sections will focus on detailed descriptions of the catalysts as well as the results achieved. Mechanistic aspects will also be included in some cases. Since the achievements in the field of catalytic enantioselective Strecker reactions reported before 2003 have already been comprehensively summarized and discussed by Gröger,^{73b} in this current review, we will mainly focus on the literature after that date. Also considering that the organocatalyzed enantioselective Strecker reactions reported before 2009 have been covered in Merino's review,^{73e} again we only present some representative examples with tables and describe in some detail a few selected highlights where necessary in order to facilitate readers.

4.1. Catalytic Enantioselective Strecker Reaction with Aldimines as Substrates

4.1.1. Chiral Oxazaborolidine Catalyst. Chiral oxazaborolidines are a class of well-known and important catalysts used in the enantioselective reduction of prochiral ketones. This class was first introduced by Itsuno et al.⁷⁴ and studied in depth by Corey et al. who successfully revealed the catalyst structure as well as the reduction mechanism.⁷⁵ Moreover, Corey and co-workers found that protonated oxazaborolidine was also an effective catalyst for the enantioselective Diels–Alder reaction⁷⁶ and cyanosilylation of aldehydes and ketones.⁷⁷ Inspired by these results, Berkessel et al.⁷⁸ studied the application of this chiral oxazaborolidine catalyst to the enantioselective Strecker reaction of *N*-benzyl imines and HCN in toluene. It was found that the oxazaborolidine **178** was the best catalyst and gave moderate results. Interestingly, the protonated oxazaborolidine **179** led to reverse chiral inductions (Scheme 48).

4.1.2. Chiral Ti(IV) Complex Catalyst. In 2007, the Feng group⁷⁹ reported a self-assembled titanium catalyst for use in Strecker reactions of aldimines and ketimines. The combined use of cinchonine **182** and 3,3'-naphthyl-2,2'-biphenol **183** with Ti(O*i*-Pr)₄ provided the optimal catalyst. It should be noted that the substituents on the 3,3'-positions of the biphenols had great impact on the enantioselectivity. In addition,

Scheme 49. Self-Assembled Ti(IV) Complex Catalyzed Enantioselective Strecker Reaction of Aldimines



i-PrOH was identified as an efficient protic additive. Under these optimized conditions (5 mol % of catalyst, 1.2 equiv of TMSCN, 1.2 equiv of *i*-PrOH, 0.2 M in toluene at -20 °C), a series of *N*-Ts-aldimines were tested. In general, high yields and ee's were obtained for a range of aromatic, aliphatic, heteroaromatic, and α,β -unsaturated substrates (Scheme 49). Moreover, CNCOOEt could be used as an alternative cyanide source giving similar results. Besides the aldimines, this catalyst was also found applicable for the asymmetric cyanation of ketimines; reaction gave excellent yields and ee values (see section 4.2.1).

The structure of the catalyst and mechanistic aspects of the reaction were also studied in detail using a combination of control experiments and NMR studies.^{79b} It was proven that sterically demanding aromatic substituents in the 3,3'-position of the biphenol were crucial to achieving the high enantioselectivity. It was shown that all the hydroxy groups in cinchona alkaloid and biphenol participated in the complexation with Ti(IV). Of note is the fact that a phenomenon of "asymmetric activation"⁸⁰ was observed for the catalyst derived from the cinchona alkaloid, 3,3'-naphthyl-2,2'-biphenol, and Ti(O*i*-Pr)₄. According to the evidence from the control experiments and the NMR studies (Figure 1) rather than adopting a *R* or *S* configuration randomly, biphenol preferred the *S* configuration on complexing. As a result, the induction ability of cinchona alkaloid, the chiral ligand, was significantly magnified by the use of an axially flexible achiral ligand, namely, biphenol. The roles of the protic additive (*i*-PrOH) and the tertiary amine in the cinchona alkaloid were also studied in detail. Results revealed that the real cyanide reagent in the catalytic cycle was in fact HCN. A bifunctional activation model was proposed (Figure 1). In addition, hydrolyzation of the cyano group of the *N*-Ts amino nitrile **181** with concentrated HCl/AcOH gave the corresponding *N*-Ts amino acid in good yield without any loss in enantiopurity.

In 2008, Hoppe et al.⁸¹ reported the synthesis of a library of *N*-arenesulfonyl-1,3-oxazolidinyl-substituted biphenyldiols **186**, which were subsequently examined as ligands in enantioselective Strecker reactions. After systematic screening, it was clear that the optimal ligands were the ones with the bulky mesitylene sulfonyl group and sterically more-demanding alkyl

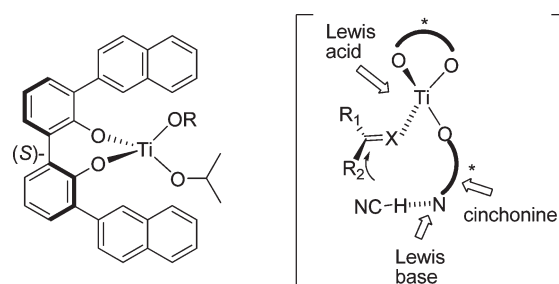


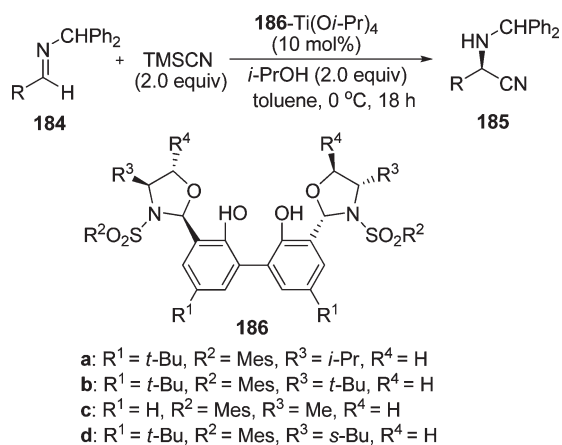
Figure 1. The preferred configuration of biphenol and the possible catalytic model.

side chains in the oxazolidine moiety. By employing 10 mol % of **186**-Ti(O*i*-Pr)₄ as the catalyst and *i*-PrOH as the additive, the Strecker reaction of various aldimines **184** proceeded well to furnish the desired products **185** with moderate to good yields and ee values (Table 5). It should be noted that the optimal ligand varied as the substrate changed. Although it appears that an overall efficient ligand has not yet been found for this system, results have revealed the advantages of designing a type of fine-tunable ligand with several variable sites that can be modified.

In 2003, Vilaivan et al. explored a series of catalysts of titanium complexes derived from chiral *N*-salicyl- β -amino alcohols for use in enantioselective catalytic Strecker reactions.⁸² It was found that the bulkiness of the substituent on the chiral β -amino alcohol played a significant role on the resulting enantioselectivity. The chiral β -amino alcohol **187** with a bulkier substituent such as Bn, *i*-Pr, *t*-Bu, or *sec*-Bu at the β -position generally gave superior results. After carefully optimizing the reaction conditions, the authors identified the optimal reaction conditions as 1.0 equiv of *N*-benzhydryl imine, 2.0 equiv of TMSCN, and 10 mol % of catalyst in toluene at 0 °C.⁸³ Under these conditions, various imines derived from aromatic aldehydes and benzhydrylamine were tested and found to furnish excellent yields and ee values (Table 6).

Interestingly, when they attempted to scale up the reaction from 0.1 to 0.5 or 1.0 mmol, they found that the reaction rate was slowed significantly. In view of the previous observations, that protic additives could greatly enhance the reaction rate without affecting the enantioselectivity, they tried some protic additives

Table 5. Chiral *N*-Arenesulfonyl-1,3-Oxazolidinyl Substituted Biphenyldiol–Ti(IV) Complex Catalyzed Enantioselective Strecker Reaction



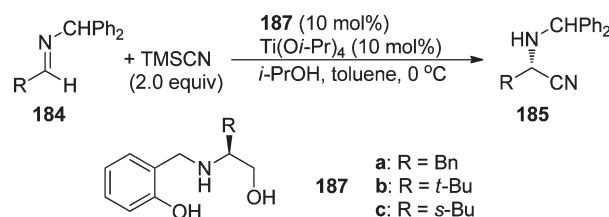
| R | ligand | yield (%) | ee (%) |
|-----------------------------------|--------|-----------|--------|
| Ph | 186b | 94 | 89 (R) |
| 4-ClC ₆ H ₄ | 186a | 87 | 84 (R) |
| 2-ClC ₆ H ₄ | 186d | 93 | 62 (R) |
| 4-MeC ₆ H ₄ | 186c | 92 | 80 (R) |
| 3-MeC ₆ H ₄ | 186a | 83 | 72 (R) |
| 2-MeC ₆ H ₄ | 186a | 91 | 85 (R) |
| <i>t</i> -Bu | 186d | 86 | 63 (R) |

such as H₂O and *i*-PrOH. It was found that in the presence of 1.0 equiv of *i*-PrOH, the Strecker reaction on the 1.0 mmol scale could go to completion within 4 h (Table 6, values in the parentheses). Further studies⁸⁴ showed that the catalyst loading could be lowered to 2.5 mol %. After a prolonged reaction time of 72 h for aromatic substrates, the corresponding products were generally obtained in excellent yields and enantioselectivities. Interestingly, in most cases *S*-configured products were produced when an *S*-ligand was used. It should be mentioned that the products were very prone to racemization in MeOH or weak acids. However, in a stronger acidic medium, such as HCl in MeOH (0.1 M), racemization of the products was completely suppressed. Based on this fact, the authors found that a HCl/TFA (1:1) mixture was efficient for the hydrolyzation of α-aryl amino nitriles to yield the optically active α-arylglycines with minimal racemization.

In 2010, Chai et al. found that the catalyst generated from *N*-salicyl-β-amino alcohol **187b** and partially hydrolyzed titanium alkoxide (PHTA) was a more efficient catalyst for asymmetric Strecker reactions.⁸⁵ PHTA was prepared by hydrolyzing Ti(On-Bu)₄ (0.5 mmol) using the residual H₂O (190 ppm) in toluene (10 mL) with stirring for 18 h. Under optimized reaction conditions, various aldimines could be converted to the corresponding adducts at room temperature in a short time, typically 15–60 min. Significantly, several kinds of *N*-protecting groups such as Ph₂CH, Bn, and Boc proved compatible with the catalyst system to give excellent results (Scheme 50).

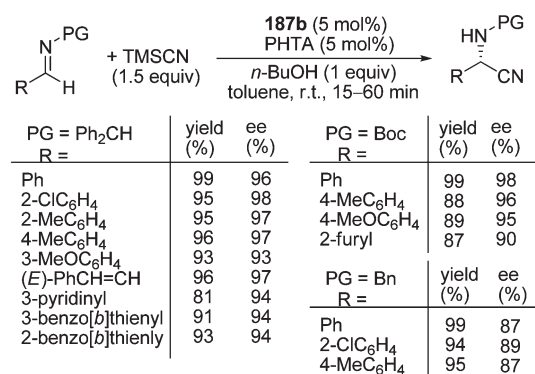
Later on, it was revealed by Chai and co-workers⁸⁶ that similar results could also be achieved by using HCN (1.2 equiv) as the cyanide reagent in the presence of catalytic amounts of TMSCN (10–25 mol %). These results are in fact very similar to those

Table 6. Chiral *N*-Salicyl-β-amino Alcohol–Ti(IV) Complex Catalyzed Enantioselective Strecker Reaction



| R | ligand | time (h) | conversion (%) | ee (%) |
|-------------------------------------------------|--------|----------|----------------|-----------|
| Ph | 187a | 48 (4) | >99 (85) | 98 (98) |
| 4-ClC ₆ H ₄ | 187a | 48 | >99 | 95 |
| 4-MeC ₆ H ₄ | 187a | 48 | >99 | 96 |
| 4-MeOC ₆ H ₄ | 187a | 48 (4) | >99 (85) | 91 (91) |
| 3-MeOC ₆ H ₄ | 187a | 48 | >99 | 94 |
| 3-NO ₂ C ₆ H ₄ | 187a | 8 | >99 | 98 |
| 2-MeC ₆ H ₄ | 187a | 48 (4) | >99 (84) | 97 (98) |
| 2-ClC ₆ H ₄ | 187a | 48 (4) | >99 (84) | 97 (97) |
| 2-BrC ₆ H ₄ | 187a | 48 (4) | >99 (80) | >98 (>98) |
| 2-MeOC ₆ H ₄ | 187a | 48 (4) | >99 (84) | 90 (83) |
| 1-naphthyl | 187a | 48 (4) | 98 (91) | 98 (>98) |
| 2-naphthyl | 187a | 48 | 97 | 96 |
| 2-furyl | 187a | 48 (4) | >99 (82) | 98 (91) |
| 2-thienyl | 187a | 48 (4) | >99 (83) | 98 (98) |
| <i>t</i> -Bu | 187c | 24 | >99 | 51 |
| PhCH=CH | 187c | 24 | >99 | 91 |

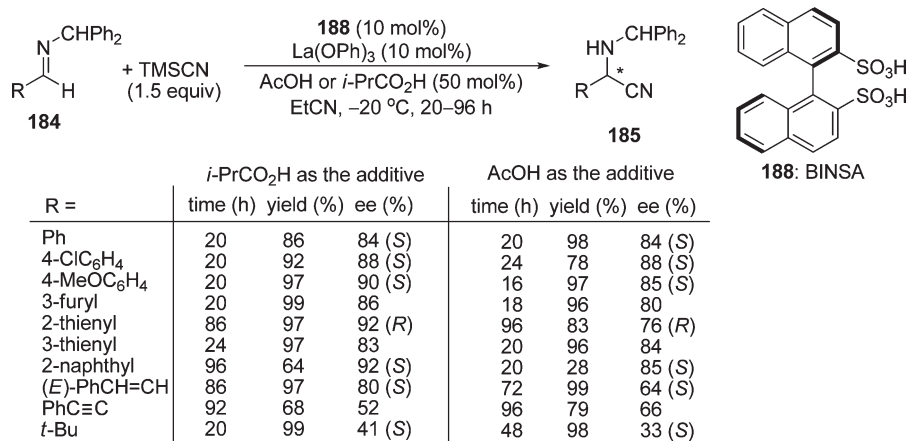
Scheme 50. Asymmetric Strecker Reaction Catalyzed by the Catalyst Generated from *N*-Salicyl-β-amino Alcohol and PHTA



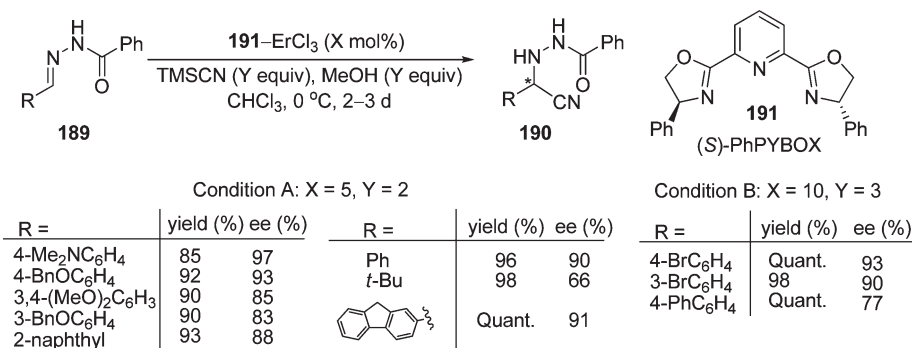
observed by the Shibasaki group⁸⁷ (see section 4.2.2). It should be noted that HCN must be slowly added over a period of 1 h after the addition of the TMSCN. Preliminary mechanistic studies indicated that TMSCN was in fact the actual cyanide reagent that was responsible for the enantioselective delivery of the cyanide ion to aldimine in the catalytic cycle. On the other hand, HCN presumably acted as the proton source to assist the release of the product while at the same time recovering the TMSCN for the next cycle.

4.1.3. Chiral Lanthanide(III) Complex Catalyst. In 2008, the Ishihara group⁸⁸ reported a novel organocatalyst, the chiral 1,1'-binaphthyl-2,2'-disulfonic acid (BINSA) **188**, for use in an

Scheme 51. Chiral Lanthanum(III)–Binaphthyldisulfonate Complex Catalyzed Enantioselective Strecker Reaction



Scheme 52. Chiral Er(III)–PYBOX Complex Catalyzed Asymmetric Hydrocyanation of Hydrazones



enantioselective direct Mannich-type reaction. Afterward, they tried to extend the scope of this catalyst to the enantioselective Strecker reaction.⁸⁹ They screened for suitable metal salts to complex with BINSAs and found that the trivalent precursor, in particular, La(OPh)₃, gave promising results. The yield and ee were further improved by adding 50 mol % AcOH or *i*-PrOH as a protic additive. It was assumed that the role of the acid additive was to transform the TMSCN into the real cyanide reagent, namely, HCN. With the optimal reaction conditions established as 10 mol % each of BINSAs and La(OPh)₃, *i*-PrCO₂H, or AcOH (50 mol %) and TMSCN (1.5 equiv) in EtCN at −20 °C, the scope of the aldimine substrates was examined (Scheme 51). The reactions with aromatic and heteroaromatic aldimines bearing electron-withdrawing and electron-donating groups proceeded in high yields with moderate to high enantioselectivities.

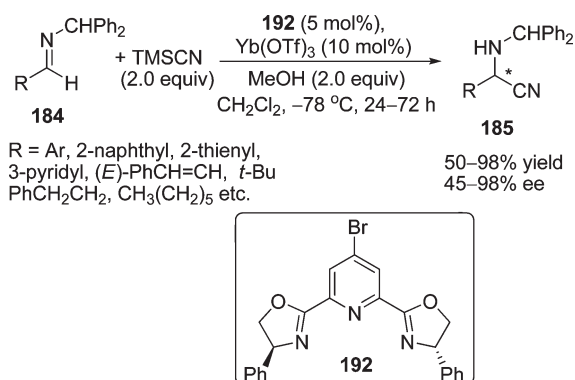
In 2004, the Jacobsen group reported the first example of a catalytic enantioselective hydrocyanation reaction of hydrazones with a (PhPYBOX)ErCl₃ complex as the catalyst.⁹⁰ A range of *N*-benzoyl-protected hydrazones **189** were successfully converted into the corresponding products **190** in high yields and good to excellent enantioselectivities (Scheme 52). It was found that the electron-deficient substrate required a higher catalyst loading as well as amounts of TMSCN and MeOH in order to achieve good reactivity and enantioselectivity.

In 2009, Karimi and Maleki developed a Yb(OTf)₃–pyridine-2,6-bis(oxazoline) catalyst for enantioselective Strecker reactions of *N*-benzhydryl aldimines **184**.⁹¹ Various reaction demands

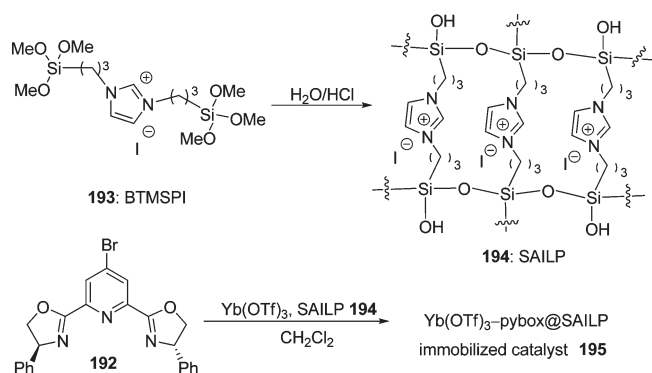
such as the need for an *N*-protecting group in the imine, judicious choice of solvent, correct ratio of Yb(III) to ligand, and an additive were all optimized in detail. The final optimal reaction conditions were found to be 5 mol % Yb(OTf)₃, 10 mol % ligand **192**, 2.0 equiv of TMSCN, and 2.0 equiv of MeOH as the additive in CH₂Cl₂ at −78 °C. Various aldimines, including aromatic, α,β-unsaturated, and aliphatic aldimines were tested under these conditions. The corresponding α-amino nitriles were obtained in excellent yields and moderate to excellent enantioselectivities (Scheme 53). Interestingly, it was shown that a Br group in the 4-position of the pyridine moiety of the ligand played a significant role in the reaction, especially on the ee of the product, without which the yield and ee dropped significantly even under the same reaction conditions.

Subsequently, the same group developed a heterogeneous catalyst **195** with Yb(OTf)₃–pybox immobilized in a novel self-assembled ionic liquid phase hybrid silica (SAILP) **194**.⁹² The self-assembled ionic liquid **194** was prepared by hydrolysis and co-condensation of 1,3-bis(3-trimethyloxysilylpropyl)-imidazolium iodide (BTMSPI) **193** under mild acidic conditions (Scheme 54). Although the catalyst **195** proved almost inactive in the Strecker reaction of the benzaldehyde derived imine under the similar reaction conditions used in the experiments described in the previous paragraph, it was found to smoothly catalyze the reaction at higher temperature of −50 °C, giving 95% yield and 80% ee after 36 h. Interestingly, the ee value was better than that obtained (53% ee) when the homogeneous catalyst Yb(OTf)₃–pybox was used.

Scheme 53. Yb(OTf)₃–PYBOX-Catalyzed Enantioselective Strecker Reaction of *N*-Benzhydryl Aldimines



Scheme 54. Preparation of Yb(OTf)₃–PYBOX Immobilized in Self-Assembled Ionic Liquid Hybrid Silica

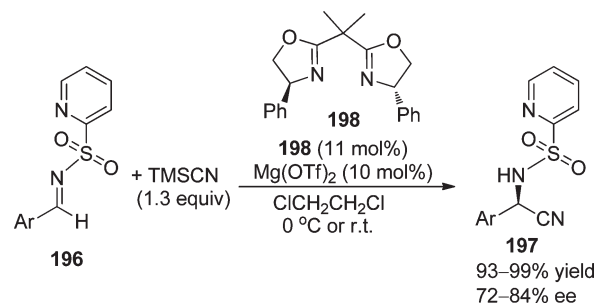


Under these optimized conditions, a series of aldimines were tested, and generally modest to good yields and ee values were obtained. It should be noted that this immobilized catalyst could be recovered and reused up to six times without loss in efficiency.

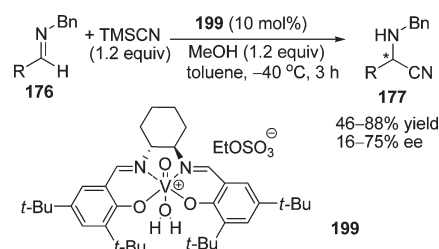
4.1.4. Chiral Mg(II) Complex Catalyst. In both 2006 and 2008, Nakamura, Toru, and co-workers⁹³ reported asymmetric Strecker reactions catalyzed by a chiral bis(oxazoline)–Mg(OTf)₂ complex. To optimize the reaction conditions, they screened various aldimines with different substituents on the nitrogen atoms of the imino groups as well as a range of Lewis acids, ligands, and solvents. The best conditions were identified as 1.0 equiv of *N*-2-pyridylsulfonyl imine, 1.3 equiv of TMSCN, 10 mol % of Mg(OTf)₂, 11 mol % of bis(oxazoline) **198** in 1,2-dichloroethane at room temperature. Excellent yields and moderate enantioselectivities were generally obtained for the series of substrates examined (Scheme 55). Although the enantioselective Strecker reaction of *N*-(2-pyridinesulfonyl)imines gave products in good yields and with good enantioselectivities, the reactions of *N*-(*p*-toluenesulfonyl)imine and of *N*-aryl- and *N*-alkylimines did not afford good results. Based on these observations, the authors assumed that the 2-pyridinesulfonyl group could act not only as an activating group but also as an efficient stereocontroller. In addition, it appears that one of the sulfonyl oxygens should be stereoselectively coordinated with the catalyst in the transition states of the reaction.

4.1.5. Chiral V(V) Complex Catalyst. In 2006, the vanadium(V)–salen complex **199**, which had previously been reported as a

Scheme 55. Chiral Bis(oxazoline)–Mg(OTf)₂ Complex Catalyzed Enantioselective Strecker Reaction of *N*-(2-Pyridinesulfonyl) Imines



Scheme 56. Chiral Salen–V(V) Complex Catalyzed Asymmetric Addition of Cyanide to *N*-Bn-Protected Aldimines



catalyst for the asymmetric synthesis of cyanohydrins,⁹⁴ was found by Crampton and North et al. to also efficiently catalyze the asymmetric addition of cyanide to *N*-Bn-protected aldimines **176**, giving α-amino nitriles **177** with up to 81% ee.⁹⁵ The protic additive MeOH proved important in enhancing both the yield and enantioselectivity. Like in many other asymmetric catalytic Strecker reactions that have been developed, the active cyanide source in the reaction system was suggested to be HCN rather than TMSCN. Having investigated various reaction conditions, the optimal conditions were identified as 10 mol % catalyst, 1.2 equiv of TMSCN, and 1.2 equiv of MeOH in toluene at -40 °C for 3 h. A range of substrates was investigated and moderate to good yields and ee values were observed (Scheme 56). In addition, these authors also used the acetophenone-derived ketimine as a substrate and obtained the product in 92% yield with an ee of 43%.

In 2010, the Khan group reported a dimeric vanadium(V)–salen complex **200**, which could catalyze asymmetric Strecker reactions of *N*-Bn-protected aldimines **176** (Scheme 57).⁹⁶ The best result was obtained using 2-methoxy-substituted aldimine as the substrate (92% yield, 94% ee). The catalyst can be precipitated and recycled by adding hexane to the post-catalytic reaction mixture.

4.1.6. Chiral Al(III) Complex Catalyst. In 2009, the Yamamoto group⁹⁷ reported a tethered bis(8-quinolinolato) aluminum complex **203** for use as a catalyst in the asymmetric Strecker reaction of the aldimines **201** with CNCOOEt as the cyanide source. They found that the reaction did not proceed with catalytic amounts of an amine base or the aluminum catalyst. This suggests that the dual activation of the electrophile and nucleophile was critical for the reaction. A survey of amines revealed DMAP and NEt₃ to be the best in terms of yield and enantioselectivity. Moreover, the

addition of 1.5 equiv of *i*-PrOH was found to be beneficial. Under these optimized conditions, a variety of aldimines were tried and overall excellent yields and enantioselectivities were obtained (Scheme 58). In addition, this catalyst can also be applied to the asymmetric Strecker reaction of ketimines using similar reaction conditions (see section 4.2.3).

In 2010, Li and co-workers reported the asymmetric Strecker reaction of *N*-phosphonyl imines **204** with Et₂AlCN.⁹⁸ Excellent yields and enantioselectivities were obtained for a variety of aromatic aldimines by using catalytic amounts of either the amino alcohol **206** or 3,3'-di-4-Ph-phenyl-BINOL **207** as the ligand (Scheme 59). The Al(III) complex generated *in situ* from the amino alcohol **206** or BINOL derivative **207** with Et₂AlCN was assumed to be the highly efficient catalyst. In addition, the *N*-protecting group can be easily cleaved with HCl (2.0 M aq.) at room temperature, and the resulting diamine recovered quantitatively.

4.1.7. Chiral Zr(IV) Complex Catalyst. The Strecker reaction was originally developed as a one-pot, three-component reaction. It was confirmed that the intermediate was imine generated from a condensation of a carbonyl compound and ammonia. Thus, to facilitate the exploitation of efficient asymmetric Strecker reactions on a small scale, imines were generally prepared beforehand in large amounts. However, for large-scale production of amino acids, the three-component reaction is far superior. While the majority of efficient enantioselective catalytic Strecker reactions are conducted with preformed imines, only a

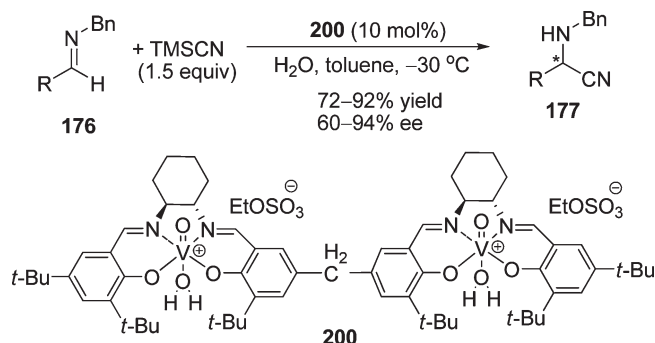
few examples are direct catalytic asymmetric three-component Strecker reactions of carbonyl compounds, amines, and cyanide reagents. Compared with the two-component reaction of imines and cyanide reagents, three-component catalytic asymmetric Strecker reactions are more difficult to perform because of two major problems. These include control of the side reaction (cyanation of carbonyl compounds) and the need to exclude the adverse effects of H₂O released as a result of imine formation.

The first successful example of a three-component Strecker reaction was reported by the Kobayashi group in 2000.⁹⁹ Before this, they had succeeded in realizing the enantioselective Strecker reaction of *N*-2-hydroxyphenyl aldimine **208** and Bu₃SnCN using the self-assembled zirconium catalyst **210**.¹⁰⁰ In a one-pot, three-component procedure, HCN was first added to the zirconium–binaphthol-based catalyst at 0 °C. This was followed by the resulting mixture being transferred to the premixed solution of aldehyde and amine at –45 °C. Both high yields and high enantioselectivities were obtained (Scheme 60). Moreover, by using a modified amine, with a methyl group in the *ortho*-position of the amino group, good results were also obtained for a series of aliphatic aldehydes.¹⁰¹

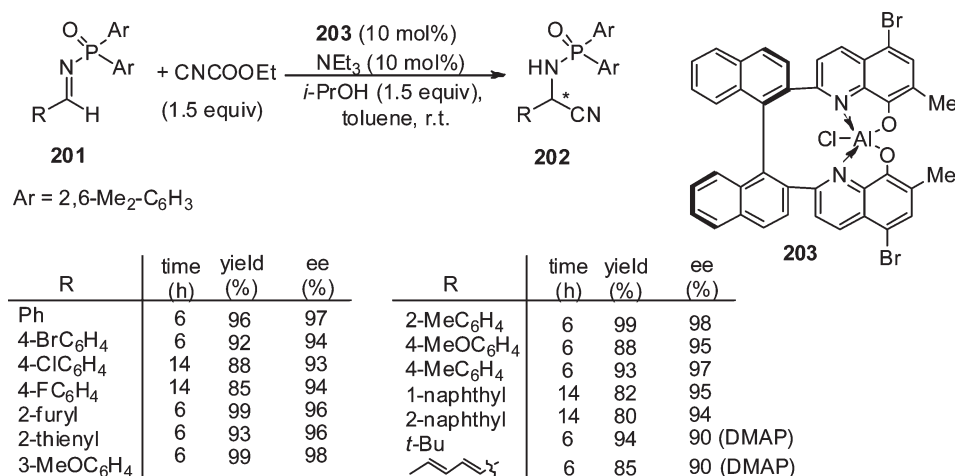
4.1.8. Chiral Organocatalysts. Asymmetric organocatalysis is a parallel approach to chiral metal-mediated reactions for obtaining chiral nonracemic α -amino nitriles. Since the Lipton group⁷² first demonstrated the chiral diketopiperazine-catalyzed hydrocyanation of aldimines in 1996, a number of chiral organocatalysts have been developed.^{73e} Among these are the protonated ammonium salts,¹⁰² phase-transfer catalysts,¹⁰³ *N*-galactosyl[2,2]-paracyclophane carbaldimines,¹⁰⁴ BINOL phosphate derivatives,^{105–110} ureas and thioureas,^{111–115} bisformamide,¹¹⁶ *N*-oxides,¹¹⁷ etc. Since a comprehensive overview of these organocatalytic Strecker reactions has been reported recently,^{73e} in addition to the representative catalysts summarized in Table 7, only the most recently developed catalysts will be described in some detail.

The chiral BINOL–phosphoric acid, which was originally reported independently by both Akiyama¹⁰⁵ and Terada,¹⁰⁶ has been demonstrated to belong to a class of powerful and versatile organocatalysts in asymmetric catalysis.¹⁰⁷ The sterically congested 3,3'-di-9-phenanthryl-BINOL-derived phosphoric acid **216a** was identified as a good catalyst for the enantioselective hydrocyanation of *N*-benzyl imines by the Rueping group¹⁰⁸ in 2006. Based on calculations, Goodman et al.¹⁰⁹ proposed a

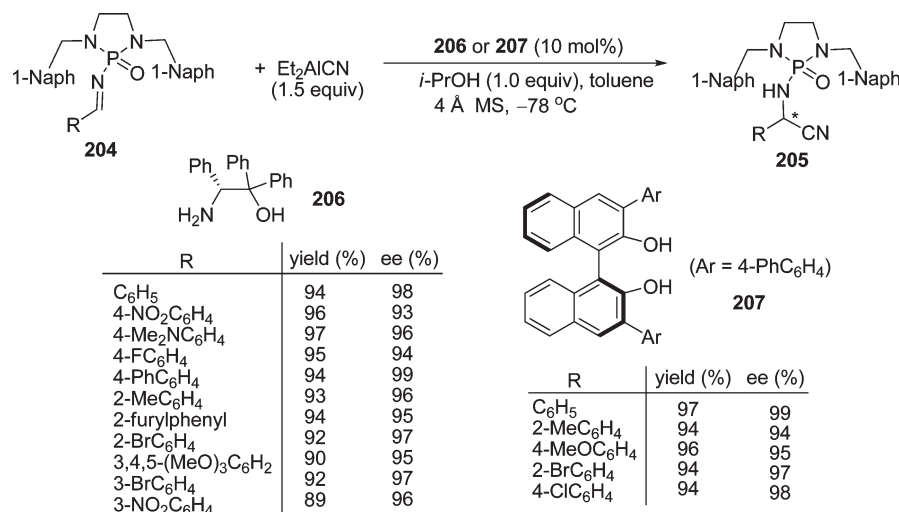
Scheme 57. Dimeric V(V)–Salen Complex Catalyzed Asymmetric Strecker Reaction of *N*-Bn Aldimines



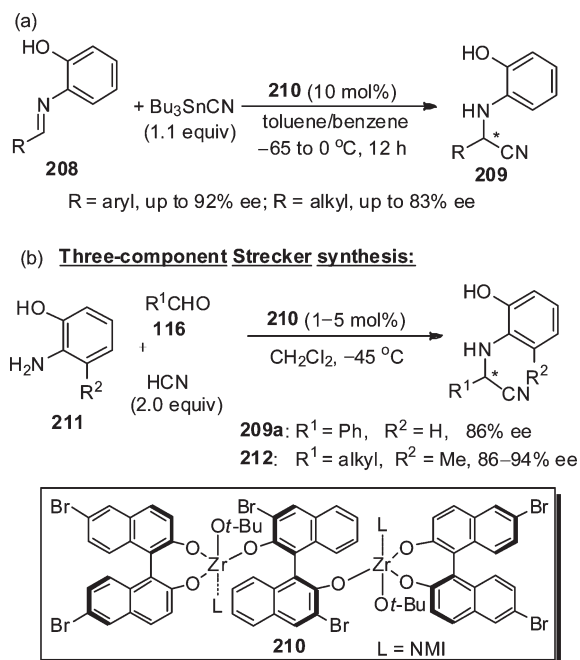
Scheme 58. Tethered Bis(8-quinolinolato)–Al(III) Complex Catalyzed Asymmetric Strecker Reaction of *N*-Phosphonyl Imines



Scheme 59. Asymmetric Strecker Reaction of *N*-Phosphonyl Imines with Et₂AlCN in the Presence of Catalytic Amounts of Amino Alcohol or BINOL Derivative



Scheme 60. Self-Assembled Zirconium Complex Catalyzed Asymmetric Three-Component Strecker Reaction of Aldehydes, Amines, and Hydrocyanide



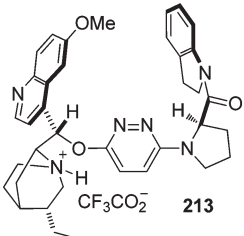
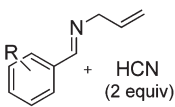
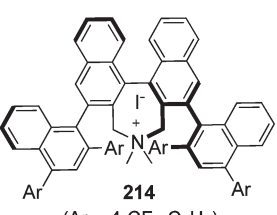
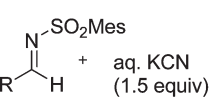
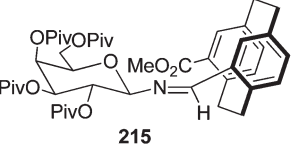
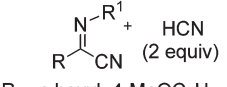
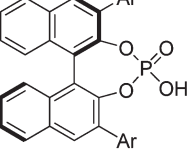
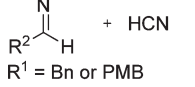
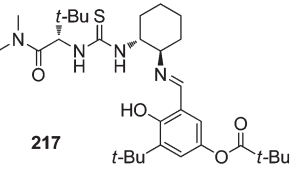
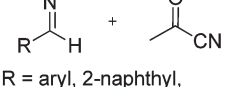
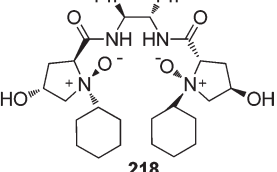
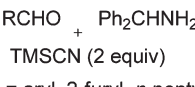
possible catalytic model for this reaction, in which the catalyst simultaneously bonded to both the imine and HCN (Figure 2).

In 2010, the Tsogoeva group used the analogous chiral BINOL–phosphoric acid **216b** for the asymmetric hydrocyanation of aliphatic aldehyde-derived hydrazones.¹¹⁰ A series of *N*-4-NO₂-benzoyl-protected aliphatic hydrazones **219** was found to perform well. The products were easily converted into the α-hydrazino acids **221** in one step and in quantitative yields (Scheme 61). Interestingly, it was found that O-silylated BINOL–phosphate generated from BINOL–phosphoric acid **216b** and TMSCN under the reaction conditions might in fact act as the actual catalyst.

From 1998 to 2002, the Jacobsen group published a series of papers on the (thio)urea catalyzed enantioselective Strecker reaction.¹¹¹ Using only 1 mol % of the catalyst **217**, *N*-Bn protected aromatic aldimines could be hydrocyanated in excellent yields and with enantioselectivities of more than 99% ee. For linear and branched aliphatic aldimines ee's of up to 96–99% were possible. In 2007, the List group explored this catalyst in the first example of an asymmetric Strecker reaction using acetyl cyanide as the cyanide reagent.¹¹² In the presence of 1–5 mol % of the catalyst **217**, acylcyanation of a range of aromatic and aliphatic aldimines **176** gave excellent yields and ee values (up to 98% ee). The catalyst was also used in the first organocatalytic three-component enantioselective Strecker reaction.^{112b} Various α-amino nitriles **194** were prepared with high yields and enantioselectivities from both aromatic and aliphatic aldehydes, amines, and acyl cyanide. Kunz et al.¹¹³ designed and synthesized an array of carbohydrate-derived urea catalysts for the asymmetric hydrocyanation of *N*-allyl aldimines with moderate to good results.

Recently, a big breakthrough was made by the Jacobsen group¹¹⁴ in the catalytic enantioselective Strecker reaction using TMSCN and KCN as the cyanide source. They identified a structurally simple, easily prepared thiourea catalyst **222**, which tolerates an extremely broad substrate range. The imines **184** derived from aryl, alkyl, heteroaryl, and alkenyl aldehydes have all proven suitable substrates (Scheme 62). Significantly, potassium cyanide combined with acetic acid could be used as the cyanide source in the presence of H₂O (Scheme 63), exhibiting great potential for the synthesis of many enantioenriched amino acids on a large scale. This procedure is particularly attractive because of the low catalyst loading, mild reaction conditions, and relatively short reaction times. Moreover, the enantioenriched amino nitriles **185** obtained were easily extended to form the *N*-Boc-protected amino acids **223** in only two steps. These involved a H₂SO₄/HCl-mediated deprotection/hydrolysis process and the Boc-protection of the free amino group with di-*tert*-butyl dicarbonate (Boc₂O). Detailed mechanistic studies were also carried out by combining experimental and computational techniques.¹¹⁵ It was suggested that rather than arising from a direct activation of the imine by the thiourea catalyst through

Table 7. Representative Organocatalytic Enantioselective Strecker Reaction of Aldimines Reported before 2009

| Catalyst and Reaction conditions | Substrate/reagent and Result | Catalyst and Reaction conditions | Substrate/reagent and Result |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p>213 10 mol% 213, CH₂Cl₂ −70 °C, 24–40 h</p> |  <p>R = H, 4-MeO, 4-Me, 4-F, 4-Br, 4-CN, 3-Me, 2-Me, 3-MeO, 3,5-Me₂ etc. 92–98% yield 79–>99% ee [102]</p> |  <p>214 (Ar = 4-CF₃-C₆H₄) 1 mol% 214, toluene/H₂O 0 °C, 2–8 h</p> |  <p>R = c-hexyl, c-Oct, <i>i</i>-Pr, <i>t</i>-Bu, Ph(CH₂)₂, (CH₃)₂CHCH₂, Ph(CH₃)₂, 1-adamantyl 81–98% yield 88–98% ee [103]</p> |
|  <p>215 34% (β-D, R [CHN]) 10 mol% 215, toluene −50 °C, 24 h</p> |  <p>R = c-hexyl, 4-MeOC₆H₄, <i>i</i>-Pr, (CH₃)₂CH(CH₂)₂ R¹ = allyl or Bn 84–89% yield 82–99% ee [104]</p> |  <p>216a (Ar = 9-phenanthryl) 10 mol% 216a toluene, −40 °C, 2–3 d</p> |  <p>R¹ = Bn or PMB R² = Aryl, 1-naphthyl, 2-naphthyl, 2-thienyl, 2-furyl, 5-Me-2-furyl 59–97% yield 85–99% ee [108]</p> |
|  <p>217 1–5 mol% 217 toluene, −40 °C, 20–50 h</p> |  <p>R = aryl, 2-naphthyl, 2-furyl, <i>i</i>-Pr, c-hexyl, <i>n</i>-Bu, <i>t</i>-Bu, <i>t</i>-BuCH₂, (<i>E</i>)-PhCH=CH 62–95% yield 89–98% ee [112]</p> |  <p>218 10 mol% 218 CH₂Cl₂, −45 °C, 30–80 h</p> |  <p>RCHO + Ph₂CHNH₂ TMSCN (2 equiv) R = aryl, 2-furyl, <i>n</i>-pentyl, <i>n</i>-Bu, <i>i</i>-Bu, <i>i</i>-Pr etc. 68–99% yield 72–95% ee [117]</p> |

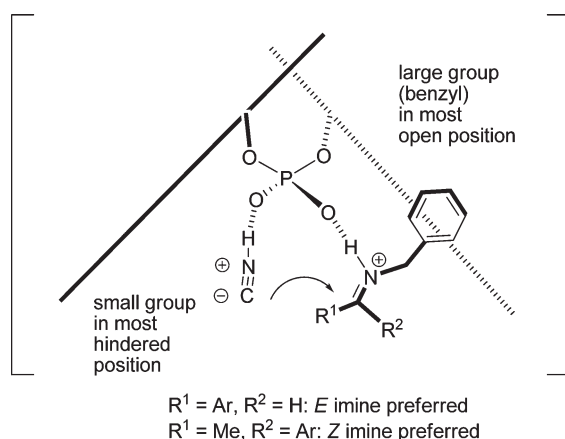


Figure 2. Proposed catalytic model

hydrogen bonding, the actual intermediate was generated from a thiourea-promoted proton transfer from hydrogen isocyanide to the imine (Figure 3). This intermediate catalyzes through multiple noncovalent interactions, and after collapse of the ion pair, the highly enantioselective α-amino nitrile is released.

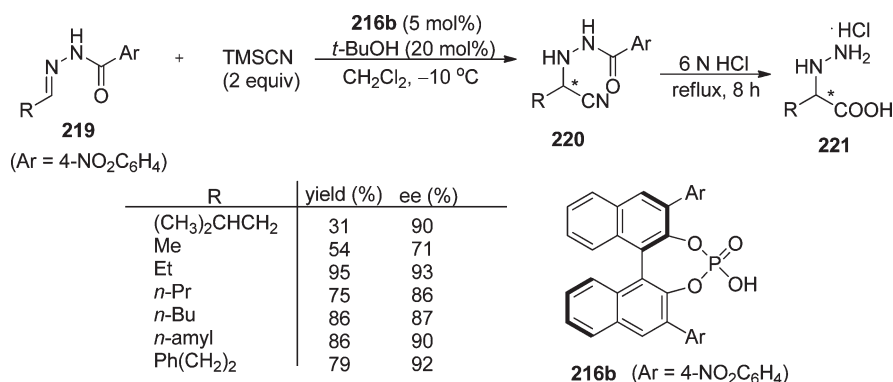
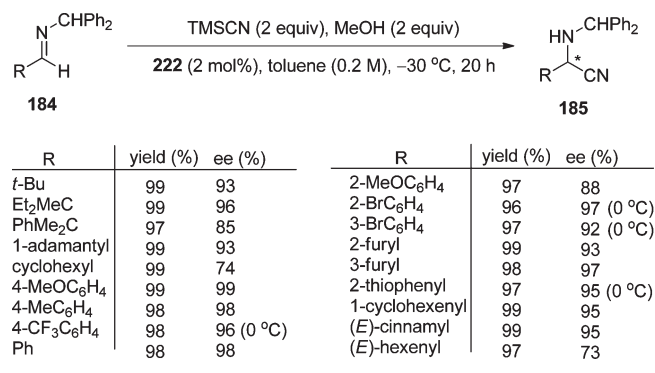
An asymmetric organocatalytic one-pot, three-component Strecker reaction was also developed by the Feng group. They initially used a C₂-symmetric bisformamide for the reaction of

aldehyde, diphenylmethanamine, and TMSCN, resulting in excellent yields with good enantioselectivities (up to 86% ee).¹¹⁶ Later, they improved these results by using a novel *N,N'*-dioxide catalyst **218** derived from diamine and *trans*-4-hydroxyl-L-proline.¹¹⁷ Both aliphatic and aromatic aldehydes were found to be suitable substrates. The corresponding α-aminonitriles were obtained in high yields with up to 95% ee.

4.2. Catalytic Enantioselective Strecker Reaction with Ketimines as Substrates

4.2.1. Chiral Ti(IV) Complex Catalyst. The first asymmetric Strecker reaction of a ketimine was reported by the Vallée group in 2000.¹¹⁸ The different catalysts they tried were titanium complex of diol derived from TADDOL or BINOL. With the BINOL–Ti(O*i*-Pr)₂ complex **224** (10 mol %) as the catalyst and tetramethylethane-1,2-diamine (TMEDA) (20 mol %) as the additive, the best result of 80% conversion and 56% ee was obtained after 1 h for the reaction of *N*-benzyl ketimine with TMSCN. Later on, they also examined the heterobimetallic scandium complex **225**, which also gave moderate results (Figure 4).¹¹⁹

As has been shown in section 4.1.2, the catalyst from cinchona alkaloid, Ti(O*i*-Pr)₄, and biphenol proved a highly efficient system for the Strecker reaction of *N*-Ts aldimines. It was also found to be highly efficient for the cyanation of *N*-Ts ketimines **226**. Excellent enantioselectivities (up to 99% ee) and high yields

Scheme 61. Chiral Phosphoric Acid Catalyzed Asymmetric Strecker Reaction of *N*-4-NO₂-Benzoyl-Protected Aliphatic Hydrazones

Scheme 62. Chiral Thiourea Catalyst for the Asymmetric Strecker Reaction of Aldimines


were achieved for a wide range of ketimines using 5–10 mol % of catalyst (Table 8). Significantly, this catalyst could also be successfully applied to the *ortho*-substituted benzophenone-derived ketimines for the preparation of quaternary α -amino nitriles with two aryl groups at the chiral center. However, although the *meta*- and *para*-substituted benzophenone-derived imines were found to give the desired products in high yields, only poor enantioselectivities were obtained. CNCOOEt was also investigated in the asymmetric Strecker reaction and excellent enantioselectivities (up to 99% ee for most of the ketimines studied) and high yields were achieved. In general, CNCOOEt showed lower reactivity than TMSCN and higher catalyst loading. Higher concentrations and longer reaction times were also required in order to achieve excellent results. Of note is the fact that in addition to the asymmetric Strecker reaction, this catalyst system also served efficiently for the asymmetric cyanation of aldehydes, ketones,^{79b} and activated olefins.¹²⁰

4.2.2. Chiral Lanthanide(III) Complex Catalyst. Followed by their wonderful achievement in the enantioselective cyanosilylation of ketones with the catalyst derived from Gd(Oi-Pr)₃ and D-glucose-derived ligand in a 1:2 ratio,¹²¹ in 2003 the Shibasaki group further extended the application of this ligand to the catalytic enantioselective Strecker reaction of *N*-diarylphosphinoyl ketimines.¹²² In the initial studies, several kinds of imines with various *N*-substituents were tested. It was found that an oxygen-containing protecting group, such as furfuryl or phosphinoyl, gave better results. This was attributed to the oxophilic

nature of the lanthanide metals. Further improvements, especially in the enantioselectivity, were achieved by using the modified glucose ligand **230**, as well as by the order in which the reagents are added. Under these optimized conditions, a series of imines **228**, derived from aromatic, aliphatic, and α,β -unsaturated ketones, were investigated. Generally, good to excellent yields and ee values were obtained (Table 9, condition A).

Interestingly, further studies showed that the addition of protic additives such as alcohols and phenols greatly benefited the outcome of the reaction.¹²³ In the presence of 2,6-dimethylphenol (DMP, 1.0 equiv), the reaction time was significantly shortened. In addition, the catalyst loading was reduced to as low as 1–2.5 mol % for a broad range of substrates (Table 9, condition B). Specifically, in addition to the substrates previously examined, the authors investigated heteroaromatic imines and cyclic imines and for the first time obtained excellent enantioselectivities and yields. Undoubtedly, this turns out to be one of the most efficient catalysts reported to date for the enantioselective catalytic Strecker reaction of ketimines.

Structural investigations of catalysts using ESI-MS indicated that the role of the protic additive 2,6-dimethylphenol (DMP) is to transform the active catalytic species **I** into **II** (Scheme 64). On the basis of this finding, it was speculated that hydrogen cyanide (HCN) might be able to play a role similar to DMP. So the authors tested the reaction using catalytic amounts of TMSCN and stoichiometric amounts of HCN (Table 9, condition C).⁸⁷ Interestingly, they demonstrated it to be working even faster, which allowed them to further lower the catalyst loading to 0.1 mol % for some acetophenone-derived substrates without affecting the yields and ee values. It should be noted that in the absence of TMSCN, the reaction did not proceed at all even with increased catalyst loading and prolonged times. This indicates that the catalytically active species **II** cannot be produced without TMSCN. In other words, **II** cannot be generated directly from the complex **V**.

As shown in Scheme 64, the authors proposed a reasonable catalytic cycle, which elucidates the reaction process. First, the imine **228** coordinates with Gd(III) in the complex **II**. Then, the cyanide combines with the other Gd(III) and enantioselectively attacks the activated imine. Intramolecular transfer of the proton then gives the desired product **229** and the complex **V**. Subsequently **V** reacts with TMSCN to form **I**, which then reacts with HCN or DMP to regenerate the catalytically active species **II**. Detailed studies on the catalyst structure have been carried out

Scheme 63. Chiral Thiourea Catalyzed Asymmetric Strecker Reaction with Aqueous KCN

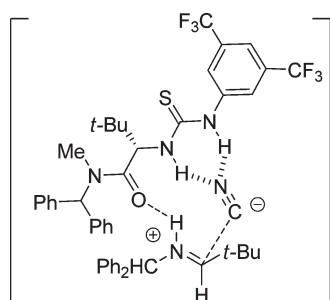
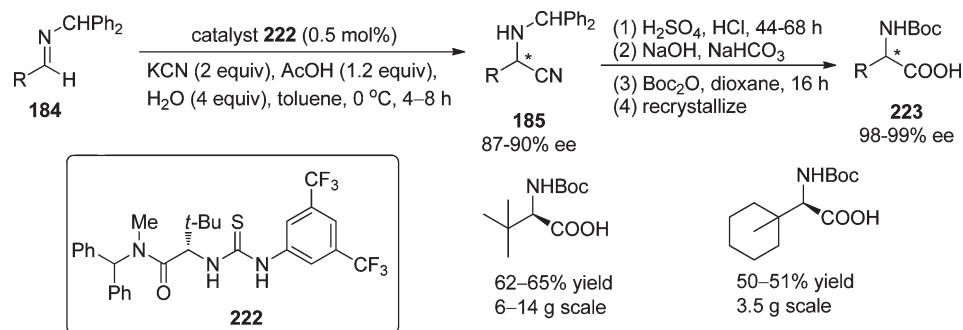


Figure 3. Proposed catalytic model.

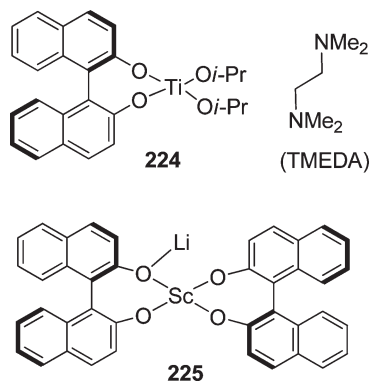


Figure 4. Chiral BINOL-derived complex catalysts.

and the exact structures were revealed by the ESI-MS results as well as the growth of single crystal of the catalyst complex.¹²⁴ It was shown that both the 2:3 and 4:5 complexes of Gd(III) and the ligand were effective catalysts for the Strecker reaction of ketimines. Most interestingly, the catalysts prepared from the same ligand and metal but by different methods exhibited totally different catalytic abilities. Not only did the reaction rates differ greatly, but the enantioselectivities also were completely inverted. This observation was attributed to the change in the assembly mode of the chiral modules. Thus, the three-dimensional characteristics of a particular catalyst were demonstrated to have a significant impact on its catalytic function.

The chiral *N*-diphenylphosphinoyl α -amino nitriles obtained were easily converted into the corresponding chiral disubstituted α -amino acids by treating with HCl (12 M). Subsequent esterification and Boc protection afforded the chiral α -amino acid derivatives in high yields.

The usefulness of this highly enantioselective catalytic Strecker reaction was confirmed by its successful application to the synthesis of (*S*)-sorbiniol **100a**. This compound is a therapeutic agent for chronic complications of diabetes mellitus (Scheme 65). With only 1 mol % of catalyst and 1 equiv of DMP, a 10 g scale Strecker reaction was performed to supply the desired α -amino nitrile **229b** quantitatively with 98% ee. Noteworthy, the enantiopure product was obtained by direct recrystallization of the crude product in 93% yield. This was then converted into (*S*)-sorbiniol by hydrolysis and hydantoin formation in three steps with a 67% yield.¹²¹ Another attractive aspect of this transformation from imine to the (*S*)-sorbiniol is that no silica gel chromatography purification is required.


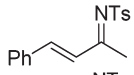
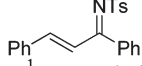
4.2.3. Chiral Al(III) Complex Catalyst. The Al(III) catalyst **203** developed by the Yamamoto group proved not only efficient for the cyanation of aldimines, as described in section 4.1.6, but suitable for ketimine substrates **231**.⁹⁷ Under reaction conditions similar to those used in the cyanation of aldimines, various *N*-protected α -amino nitriles **232** with quaternary stereocenters were prepared in a highly enantioselective manner with good to excellent yields and ee values (Scheme 66).

4.2.4. Chiral Organocatalysts. As a result of subtle structural changes, the organocatalysts, which were found useful for the cyanation of aldimines, also gave good stereochemical outcomes in the Strecker reaction of ketimines. Examples including chiral (thio)ureas,^{111d,125} *N,N'*-dioxides,^{126–129} and phosphate derivatives^{130–133} that have already been discussed in previous reviews are summarized in Table 10.^{73e}

The first example of this type of reaction was reported by the Jacobsen group in 2000.^{111d} Using 2 mol % of the urea catalyst **233a**, they showed that some *N*-allyl, Bn, or *para*-substituted benzyl protected ketimines could react with HCN efficiently at -75 °C.^{111d} Significantly, the catalyst could be easily recovered and reused and even showed identical catalytic properties to that of a freshly prepared one. The resin-bound catalyst **233b** was also investigated. The reactivity could be enhanced without affecting the enantioselectivity by using a higher catalyst loading and carrying out the reaction at -40 °C. This approach proved more convenient because the catalyst was more easily separated after reaction and could be recycled from the reaction mixture.

Very recently, Enders and co-workers reported the thiourea-catalyzed enantioselective Strecker reaction of *N*-PMP (*p*-methoxyphenyl)-protected trifluoromethyl ketimines **236** with TMSCN.¹²⁵ Takemoto's thiourea catalyst **238** proved the most efficient for a range of substrates (Scheme 67). Although the reaction proceeded sluggishly (5–27 days), generally good to

Table 8. Substrate Scope for the Cyanation of *N*-Ts Ketimines with TMSCN

| ketimine | catalyst loading (mol %) | time (h) | yield (%) | ee (%) |
|-------------------------------------------------------------------------------------|--------------------------|----------|-----------|----------------------|
| $R^1 = \text{Ph}, R^2 = \text{Me}$ | 5 | 4 | >99 | >99(<i>S</i>) |
| $R^1 = 4\text{-FC}_6\text{H}_4, R^2 = \text{Me}$ | 5 | 4 | 90 | 98 |
| $R^1 = 4\text{-ClC}_6\text{H}_4, R^2 = \text{Me}$ | 5 | 4 | >99 | >99(<i>S</i>) |
| $R^1 = 4\text{-BrC}_6\text{H}_4, R^2 = \text{Me}$ | 5 | 8 | >99 | >99(<i>S</i>) |
| $R^1 = 4\text{-MeC}_6\text{H}_4, R^2 = \text{Me}$ | 10 (5) | 4 (50) | >99 (91) | >99(94)(<i>S</i>) |
| $R^1 = 4\text{-MeOC}_6\text{H}_4, R^2 = \text{Me}$ | 10 (5) | 4 (50) | 99 (95) | >99 (94)(<i>S</i>) |
| $R^1 = 3\text{-ClC}_6\text{H}_4, R^2 = \text{Me}$ | 5 | 4 | >99 | >99 |
| $R^1 = 2\text{-FC}_6\text{H}_4, R^2 = \text{Me}$ | 10 (5) | 4 (24) | >99(>99) | 90 (84) |
| $R^1 = 2\text{-naphthyl}, R^2 = \text{Me}$ | 5 | 22 | 90 | >99(<i>S</i>) |
|  | 10 (5) | 51(50) | 99 (76) | 82 (70)(<i>S</i>) |
| $R^1 = 2\text{-furyl}, R^2 = \text{Me}$ | 5 | 22 | 97 | 99 |
| $R^1 = 2\text{-thienyl}, R^2 = \text{Me}$ | 5 | 22 | 97 | >99 |
| $R^1 = \text{Ph}, R^2 = \text{Et}$ | 10 (5) | 4 (4) | >99 (66) | >99 (74) |
| $R^1 = \text{Ph}, R^2 = n\text{-Pr}$ | 10 (5) | 4 (45) | 69 (93) | >99 (64) |
| $R^1 = \text{Ph}, R^2 = \text{cyclohexyl}$ | 10 | 48 | - | - |
|  | 5 | 17 | 97 | 98 |
|  | 10 | 20 | >99 | 71 |
| $R^1 = \text{cyclohexyl}, R^2 = \text{Me}$ | 10 (5) | 4 (4) | >99 (77) | 94 (80) |
| $R^1 = t\text{-Bu}, R^2 = \text{Me}$ | 10 (5) | 4 (4) | 98 (77) | 69 (65) |
| $R^1 = 2\text{-FC}_6\text{H}_4, R^2 = \text{Ph}$ | 10 | 5 | 96 | 98 |
| $R^1 = 2\text{-ClC}_6\text{H}_4, R^2 = \text{Ph}$ | 10 | 45 | 95 | 97 |
| $R^1 = 2\text{-MeC}_6\text{H}_4, R^2 = \text{Ph}$ | 10 | 45 | 90 | 97 |

excellent yields and enantioselectivities were achieved for a variety of trifluoromethyl ketimines. Also, as demonstrated by the authors, the optically active α -amino nitriles obtained could be easily converted into the corresponding, therapeutically important α -quaternary, α -trifluoromethyl amino acids after deprotection and hydrolysis of the cyano function (Scheme 68).

The Feng group continued to use the *N*-oxide catalysts¹²⁶ in Strecker reactions of ketimines. *In situ* generated N,N' -dioxide from the bispeiperinamide **234** and *m*-CPBA proved efficient for the enantioselective cyanosilylation of the *N*-diphenylphosphinoyl ketimines **228** under mild reaction conditions.¹²⁷ The N,N' -dioxide **235**, derived from *L*-prolineamide and isophthalaldehyde, catalyzed the asymmetric Strecker reaction of *N*-Ts ketimines **226** with moderate to good results.¹²⁸ Because the linkers used to connect the two *N*-oxide moieties in the previously designed N,N' -dioxides were achiral, it seemed pertinent to synthesize and investigate a series of N,N' -dioxides with chiral linkers. A breakthrough for the reaction of *N*-Ts ketimines **226** was achieved by using N,N' -dioxide **239** with a sterically rigid

chiral BINOL backbone.¹²⁹ With 1-adamantanol as the additive, a wide range of ketimines such as aryl methyl imines, heteroaromatic imines, aliphatic imines, cyclic imines, and diphenyl imine were successfully transformed into the desired products in excellent yields and enantioselectivities (Scheme 69). The features of this method included low catalyst loading, mild reaction conditions, and excellent enantioselectivities. In addition, by comparing the performance of the N,N' -dioxides **235**, the superior performance as a result of introducing the axial chiral BINOL scaffold into the catalyst structure was evident. Overall it made the asymmetric induction more efficient.

The potential and development of efficient three-component asymmetric Strecker reactions of ketimines is an ongoing research challenge. Several efficient methods have already been documented for the synthesis of racemic α -quaternary amino nitriles from ketones, amines, and a cyanide reagent.¹³⁰ However, to date there is only one report that attempted the asymmetric variant of this reaction. In 2010, the Ma group reported an efficient method for the one-pot, three-component Strecker reaction of ketimines employing a BINOL-derived phosphoric

Table 9. Enantioselective Strecker Reaction of *N*-Diphenylphosphinoyl Ketimines Catalyzed by the Complex of Gd(*Oi*-Pr)₃ and D-Glucose-Derived Ligand

| $ \begin{array}{ccc} \text{R}_1\text{C}(\text{R}_2)\text{N}=\text{P}(\text{O})\text{Ph}_2 & \xrightarrow[\text{CH}_3\text{CH}_2\text{CN}, -40\text{ }^\circ\text{C}]{\text{condition A-C}} & \text{R}_1\text{C}(\text{R}_2)\text{H}\text{N}-\text{P}(\text{O})\text{Ph}_2 \\ \text{228} & & \text{229} \end{array} $ | | | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-----------|----------|-----------|--------|
| <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="border: 1px solid black; padding: 5px; text-align: center;"> x mol% Gd(<i>Oi</i>-Pr)₃ 2x mol% 230 (x = 2.5–10) TMSCN (1.5 equiv) </div> <div style="border: 1px solid black; padding: 5px; text-align: center;"> x mol% Gd(<i>Oi</i>-Pr)₃ 2x mol% 230 (x = 1–2.5) 2,6-dimethylphenol (1.0 equiv) TMSCN (1.5 equiv) </div> <div style="border: 1px solid black; padding: 5px; text-align: center;"> x mol% Gd(<i>Oi</i>-Pr)₃ 2x mol% 230 (x = 0.1–5) 2.5–20 mol% TMSCN HCN (1.5 equiv) </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> condition A condition B condition C </div> | | | | | |
| <div style="display: flex; align-items: center;"> <div style="text-align: center; margin-right: 10px;"> <p>230</p> </div> </div> | | | | | |
| substrate | condition | X (mol %) | time (h) | yield (%) | ee (%) |
| | A | 2.5 | 24 | 94 | 95 |
| | B | 2.5 | 2 | 98 | 97 |
| | C | 0.1 | 19 | 97 | 90 |
| | A | 2.5 | 67 | 84 | 89 |
| | B | 2.5 | 0.7 | 90 | 97 |
| | C | 0.1 | 54 | 99 | 93 |
| | C | 1 | 0.6 | 99 | 95 |
| | A | 10 | 14 | 72 | 85 |
| | B | 2.5 | 2 | 97 | 93 |
| | A | 5 | 65 | 73 | 72 |
| | B | 5 | 2 | 96 | 93 |
| | A | 5 | 52 | 99 | 88 |
| | B | 5 | 2 | 94 | 94 |
| | A | 5 | 68 | 79 | 83 |
| | B | 5 | 0.2 | 95 | 98 |
| | B | 1 | 38 | 93 | 96 |
| | B | 1 | 22 | 92 | 92 |
| | B | 2.5 | 0.3 | 94 | 98 |
| | B | 2.5 | 1.3 | 98 | 99 |
| | C | 1 | 3 | 99 | 99 |
| | C | 5 | 21 | 0 | - |
| | C | 2.5 | 0.3 | 92 | 99 |
| | B | 5 | 0.25 | 99 | 94 |

acid as the catalyst.¹³¹ A wide range of racemic α -amino nitriles with different substituents were synthesized in high yields from various ketones and substituted anilines under mild conditions. In an effort to make the reaction enantioselective, they investigated some 3,3'-disubstituted BINOL-derived phosphoric acids. Although only up to 40% ee was obtained in their preliminary studies with **216a** as the catalyst, this catalyst system holds great potential for attaining a highly

enantioselective three-component Strecker reaction of ketimines (Scheme 70).

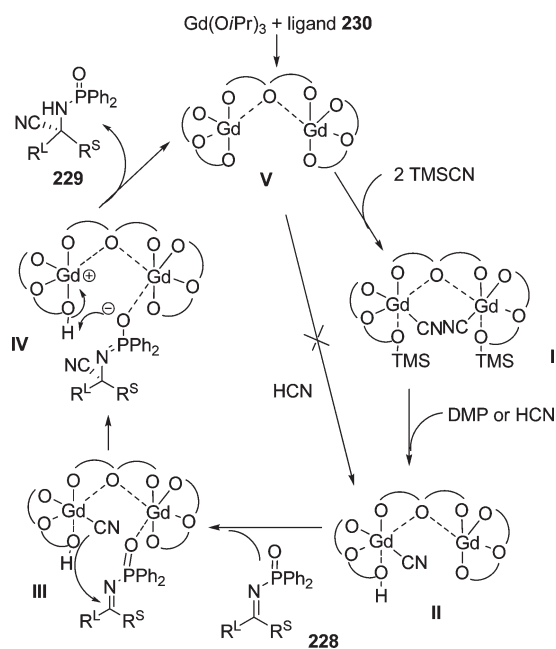
Instead of utilizing phosphoric acids as Brønsted acid catalysts,¹³² in 2009, the Feng group found that the unsubstituted (*S*)-BINOL-derived phosphoric acid sodium salt could serve as a highly efficient catalyst for the enantioselective Strecker reaction of the *N*-diphenylphosphinoyl-protected ketimines **228** (Scheme 71).¹³³ They found that

using 2-(1-adamantyl)-4-(*t*-Bu)-phenol as the additive (10 mol %) was crucial for improving the enantioselectivity. A variety of ketimines were examined under mild reaction conditions, and the adducts were obtained in yields and ee of up to 96% and 95%, respectively. Interestingly, when HCN was employed as the cyanide source instead of TMSCN, the reaction proceeded very sluggishly, and no enantioselectivity was observed.

4.3. Catalytic Enantioselective Strecker Reaction with Imine Equivalents as Substrates

For the first time in 2004, the Vilaivan group¹³⁴ described the synthesis of *N*-protected α -amino nitriles from *N*-protected α -amido sulfones¹³⁵ by treating with 2 equiv of potassium cyanide in *i*-PrOH or CH₂Cl₂/H₂O under phase-transfer conditions. Two years later, Herrera, Ricci, and co-workers¹³⁶ used the quinine-derived phase-transfer catalyst **244** for the enantioselective Strecker reaction of the α -amido sulfones **242** with cyanohydrins **88**. Moderate to good yields and ee values were obtained (Scheme 72). This is the first example of using cyanohydrin as the cyanide source in asymmetric organocatalyzed Strecker reactions performed under phase transfer conditions and employing *N*-Boc-protected α -amido sulfones as the imine precursors. As far as the mechanistic aspects were concerned, the authors proposed that the deprotonated cyanohydrin could act as the base to transform the sulfone into the corresponding imine that would be subsequently and quickly attacked by the cyanide ion surrounded by the chiral catalyst.

Scheme 64. Proposed Reaction Mechanism



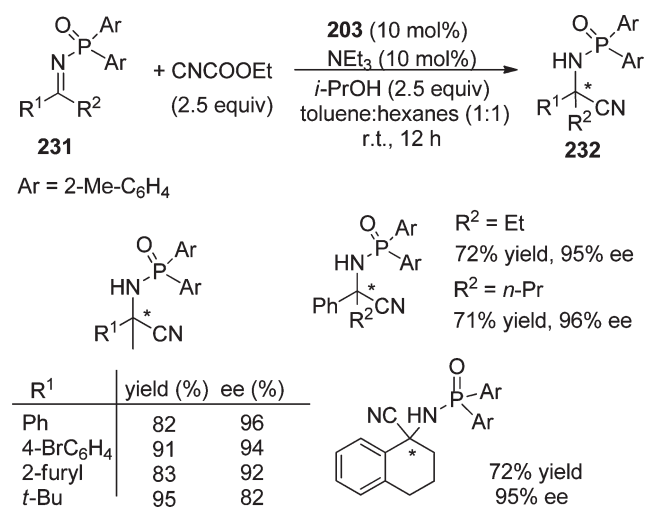
In 2007, the Maruoka group¹³⁷ reported a highly enantioselective synthesis of *N*-arylsulfonyl α -amino nitriles **246** from the corresponding α -amido sulfones **245** with the chiral quaternary ammonium iodide **214** as the efficient phase-transfer catalyst. It should be noted that by using only 1 mol % catalyst and 1.05 equiv of KCN (2 M in H₂O), a series of aliphatic chiral α -amino nitriles **246** could be obtained in excellent yields and ee's within 2 h (Scheme 73). Moreover, compared with their previous studies using preformed imines, it has been demonstrated that the *in situ* generation of the reactive *N*-sulfonyl imines was advantageous for the cyanation of the substrates having primary and secondary alkyl substituents, especially with respect to the yield.

In 2009, Bräse et al.¹³⁸ reported another enantioselective Strecker reaction using the α -amido sulfones **247** as the starting material and catalyzed by 5 mol % quinine **249** in the presence of 2.0 equiv of KCN. Good yields and moderate ee values were obtained for the aromatic substrates examined (Scheme 74). Their attempt to extend the scope to aliphatic substrates was unsuccessful. Some other *N*-carbamoyl groups were also examined. As can be seen from Scheme 74, both the yields and ee values were closely related to the nature of the *N*-substituents. In some cases, the configurations of the products were totally reversed.

5. SUMMARY AND OUTLOOK

Due to the vital role played by amino acids in various scientific areas such as organic synthesis, medicinal chemistry,

Scheme 66. Tethered Bis(8-quinolinolato) Aluminum Complex Catalyzed Asymmetric Strecker Reaction of *N*-Diarylmethyl Ketimines



Scheme 65. Asymmetric Synthesis of (*S*)-Sorbinil with Catalytic Enantioselective Strecker Reaction as the Key Step

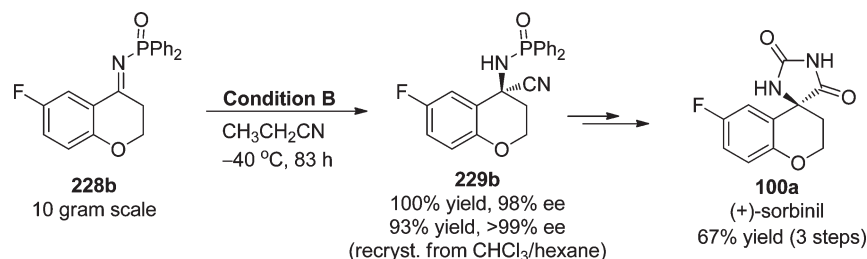
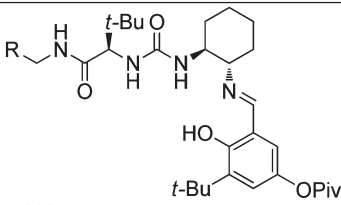
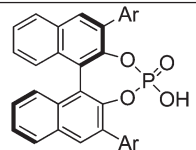
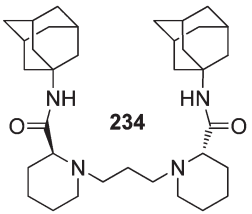
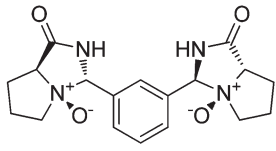
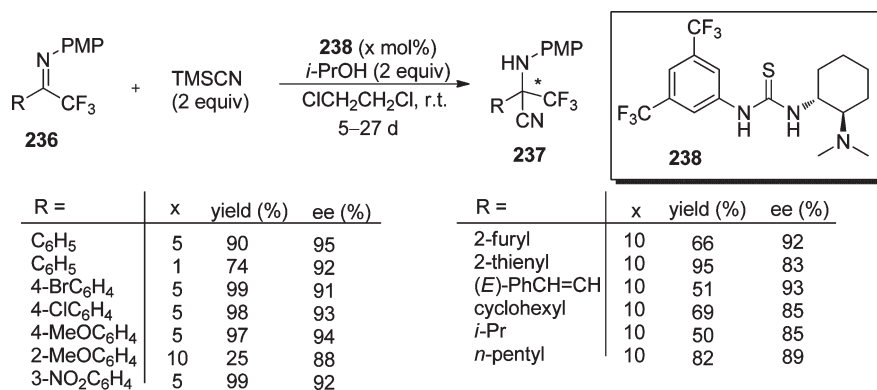
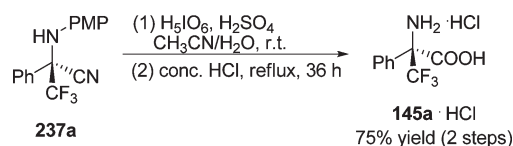


Table 10. Representative Organocatalytic Enantioselective Strecker Reaction of Ketimines Reported before 2009

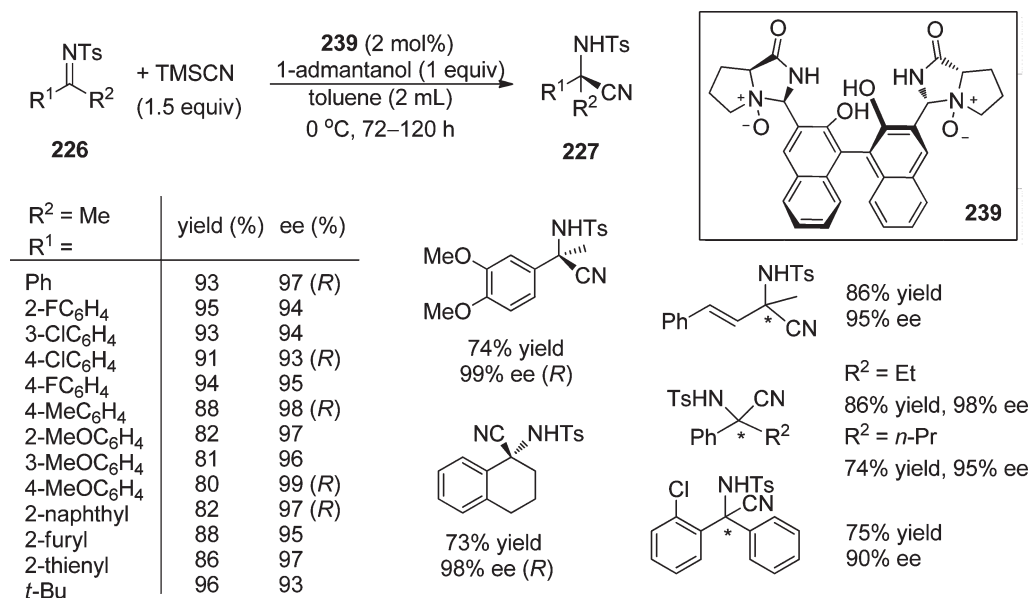
| Catalysts and Reaction Conditions | Substrate/Reagent and the Results | Catalysts and Reaction Conditions | Substrate/Reagent and the Results |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p>233a: R = Ph 233b: R = polystyrene 2 mol% 233a, toluene, -75 °C</p> | $\text{R}^1\text{C}(\text{R}^2)=\text{N}-\text{R}^2 + \text{HCN}$ R ² = allyl 97% yield, 85–89% ee R ² = Bn 45–>99% yield, 42–95% ee [111d] |  <p>216a (Ar = 9-phenanthryl) 5 mol% 216a toluene, -40 °C, 3d</p> | $\text{Ar}-\text{C}(\text{R})=\text{N}-\text{R} + \text{HCN}$ R = 4-BrC ₆ H ₄ up to 90% yield, 80% ee R = 4-MeOC ₆ H ₄ up to 95% yield, 72% ee [132] |
|  <p>234 5 mol% 234 10 mol% <i>m</i>-CPBA toluene, -20 °C, 60–196 h</p> | $\text{R}^1\text{C}(\text{R}^2)=\text{N}-\text{P}(\text{O})\text{Ph}_2 + \text{TMSCN (1.5 equiv)}$ R ¹ = aryl, 2-naphthyl, <i>t</i> -Bu, 2-thienyl, 2-pyridyl R ² = Me, <i>n</i> -Pr etc. 90–98% yield, 72–92% ee [127] |  <p>235 5 mol% 235, 20 mol% additive toluene, -20 °C, 68–80 h</p> | $\text{R}-\text{C}(\text{NTs})=\text{N}-\text{R} + \text{TMSCN (1.5 equiv)}$ R = aryl, 2-thienyl, <i>c</i> -hexyl, <i>t</i> -Bu 91–99% yield, 71–91% ee [128] |

Scheme 67. Thiourea-Catalyzed Enantioselective Strecker Reaction of *N*-PMP-Protected Trifluoromethyl KetiminesScheme 68. Conversion of Optically Active α -Amino Nitrile to Quaternary α -Trifluoromethyl Amino Acid

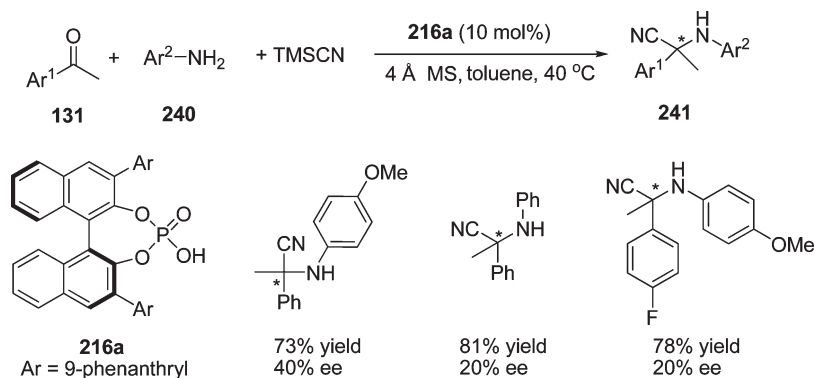
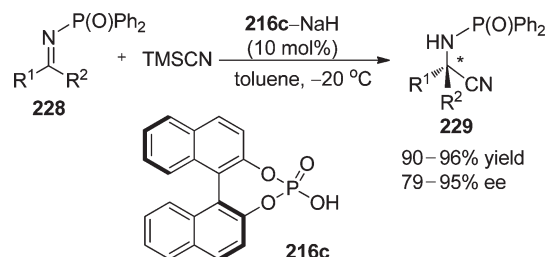
biochemistry, and pharmaceutical science, the Strecker reaction is recognized as among the most significant and useful reactions in organic chemistry. Both asymmetric Strecker reactions, using chiral nonracemic imines, and enantioselective catalytic Strecker reactions have been demonstrated as valuable pathways for synthesizing a diverse range of chiral optically active α -amino acids. Although in most reports

preformed imines were used as substrates in asymmetric Strecker reactions, some other important strategies, including the asymmetric three-component Strecker reaction and the use of α -amido sulfones as precursors of the corresponding imines, have also been developed.

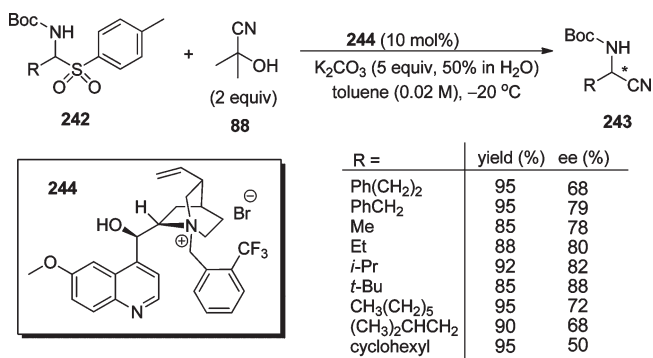
In addition to imines, some other imine-like substrates such as hydrazones, nitrones, and iminium salts have also been studied in asymmetric Strecker-type reactions. However, most of them were used in their chiral nonracemic forms for the purpose of achieving substrate-based chiral induction. To the best of our knowledge, except for hydrazones, there are still no reports using other imine-like substrates in the catalytic enantioselective cyanide addition reaction. The Reissert reaction, which involves quinoline as the substrate, is another reaction closely related to the Strecker reaction.¹³⁹ By using benzoyl chloride to react with quinoline in order to

Scheme 69. Enantioselective Strecker Reaction of *N*-Ts Ketimines Catalyzed by *N,N'*-Dioxide with Axially Chiral BINOL Backbone

Scheme 70. Three-Component Asymmetric Strecker Reaction of Ketimines

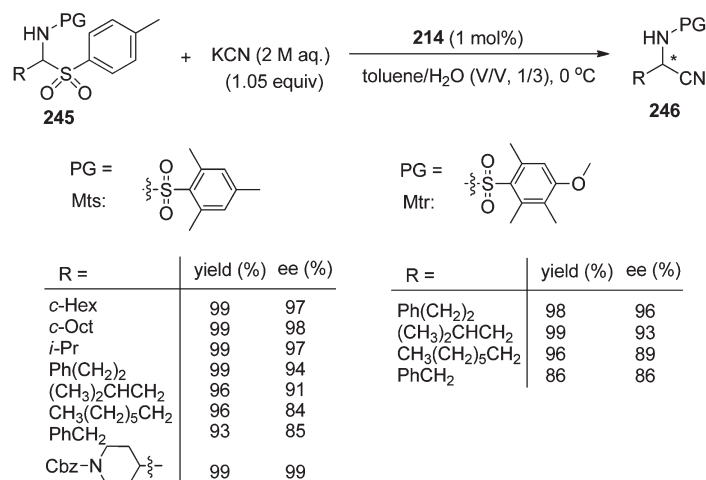
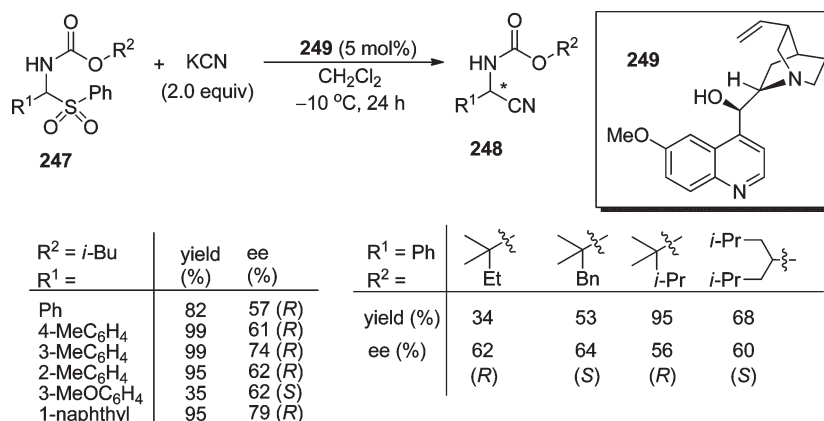
Scheme 71. BINOL-Derived Phosphoric Acid Sodium Salt Catalyzed Enantioselective Strecker Reaction of *N*-Diphenylphosphinoyl Ketimines

Scheme 72. Phase-Transfer Catalyst Promoted Enantioselective Conversion of α-Amido Sulfones to α-Amino Nitriles with Cyanohydrin



form the *N*-acyl quinonium chloride salt, the cyanide can add smoothly to the activated C=N bond. The first catalytic enantioselective Reissert reaction was reported by the Shibasaki group in 2000. They used the highly efficient BINOL-derived bifunctional aluminum catalyst.¹⁴⁰ Afterward, they

also succeeded in expanding the substrate range to various substituted isoquinolines and pyridines by using a similar

Scheme 73. Phase-Transfer Catalyst Catalyzed Enantioselective Conversion of α -Amido Sulfones to α -Amino Nitriles with KCNScheme 74. Quinine-Catalyzed Enantioselective Conversion of α -Amido Sulfones to α -Amino Nitriles

group of catalysts.¹⁴¹ This methodology has proven extremely useful for the syntheses of some key pharmaceutically important intermediates and has been well summarized and discussed in several reviews.¹⁴²

For catalytic enantioselective Strecker reactions, many types of catalysts are now available: various metal complexes, phase-transfer catalysts, chiral salts, Brønsted acids, Lewis bases, (thio)urea, and others. In some cases, a high catalytic capability could be achieved with very low catalyst loading, and even water can be used as the cosolvent. Some catalysts are recyclable without loss of catalytic ability and enantioselectivity. By successfully employing some relatively safe yet inexpensive cyanide donors such as KCN and CNCOOEt, researchers have recently achieved some highly efficient and enantioselective catalytic Strecker reactions that show great potential for large scale and industrial use. Excitingly, some catalyst systems have been shown to be applicable for the asymmetric Strecker reaction of both aldimines and ketimines. Thus, clearly the development of a simple and robust catalyst having a wide substrate scope is not only interesting

but highly desirable. Given that there are fewer catalyst systems for the asymmetric Strecker reaction of ketimines than for that of aldimines and that the three-component reactions of ketones, amines, and cyanide donors are still rare, more research effort needs to be expended in this area.

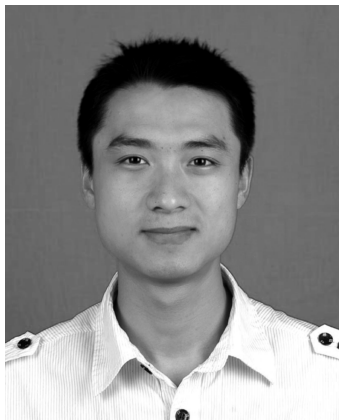
To conclude, although there are many different ways we can contribute to this fantastic research area, such as developing chiral auxiliary or asymmetric catalysis strategies, exploring different kinds of catalysts, attempting novel three-component procedures, evaluating imines with different protecting groups, and employing various cyanide reagents, clearly the common goal is trying to make the asymmetric Strecker reaction more convenient, practical, economic, and efficient. We are confident that one day, with cheaper and more easily available chiral catalysts, a broad range of chiral α -amino nitriles will be prepared with higher yields and better enantioselectivities, with lower catalyst loadings, and in shorter reaction times under milder reaction conditions. It is hoped that this overview of what is undoubtedly an exciting and challenging area will prove useful.

AUTHOR INFORMATION

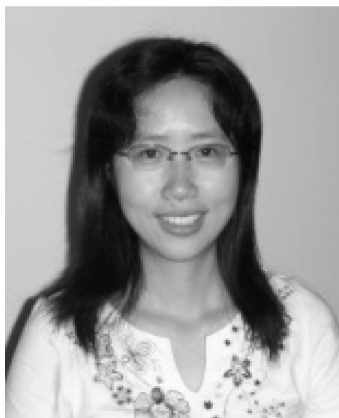
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Xiaohua Liu was born in Hubei, China. She received her B.S. degree from Hubei Normal University in 2000. Then she studied chemistry at Sichuan University and received her M.S. degree under the supervision of Professor Jiayuan Hu in 2003 and her Ph.D. under the supervision of Professor Dr. Xiaoming Feng in 2006. She was appointed as an associate professor in 2006 and joined Professor Dr. Feng's group. Her current research interests cover asymmetric catalysis and organic synthesis.



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