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Recent Developments in Catalytic Asymmetric Strecker-Type Reactions

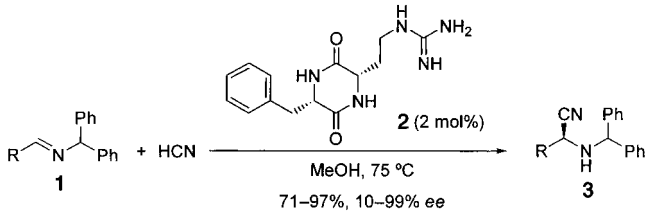
Larry Yet*

The Strecker amino acid synthesis, which involves treatment of aldehydes with ammonia and hydrogen cyanide (or equivalents) followed by hydrolysis of the intermediate α-aminonitriles to provide α-amino acids (Scheme 1), was first

Scheme 1. Classical Strecker synthesis of α-amino acids.

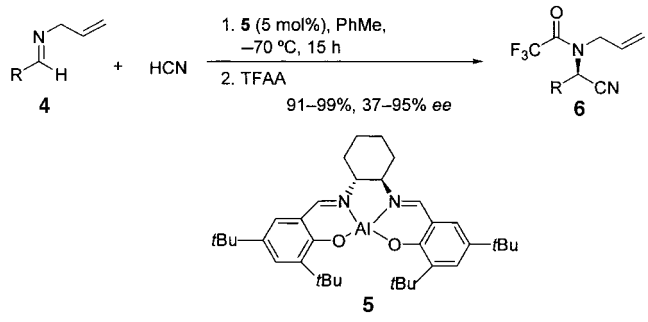
reported in 1850.[1] This method has been applied on an industrial scale toward the synthesis of racemic α-amino acids, but more recently interest in nonproteinogenic α-amino acids in a variety of scientific disciplines has prompted intense activity in the asymmetric syntheses of α-amino acids.[2] The catalytic asymmetric Strecker-type reaction offers one of the most direct and viable methods for the asymmetric synthesis of α-amino acid derivatives. It is the purpose of this Highlight to disclose recent developments in this emerging field of importance.

Lipton and co-workers investigated the viability of the asymmetric Strecker amino acid synthesis in which they utilized cyclic guanidine dipeptide **2** in the reaction of *N*-benzhydrylimines **1** with hydrogen cyanide to give *N*-benzhydryl-α-aminonitriles **3** (Scheme 2).[3] *N*-Benzhydrylimines **1**, derived from aromatic aldehydes, gave products **3** in generally high enantiomeric excess. However, electron-deficient 3-nitro, 3-pyridyl, and aliphatic aldehyde derivatives afforded racemic products.



Scheme 2. Asymmetric Strecker synthesis with cyclic dipeptide **2** (Lipton and co-workers).

Sigman and Jacobsen reported the first example of a metal-catalyzed enantioselective Strecker-type reaction using a chiral Al^{III}–salen complex (salen = *N*,*N*′-bis(salicylidene)-ethylenediamine dianion).[4] A variety of *N*-allylimines **4** were evaluated in the reaction catalyzed by complex **5** to give products **6**, which were isolated as trifluoroacetamides in good yields and moderate-to-excellent enantioselectivities (Scheme 3). Substituted arylimines **4** were the best substrates,



Scheme 3. Asymmetric Strecker synthesis with chiral Al^{III}–salen catalyst **5** (Sigman and Jacobsen). TFAA = trifluoroacetic anhydride.

while alkyl-substituted imines afforded products with considerably lower *ee* values. Jacobsen and co-workers also reported that non-metal Schiff base catalysts **8** and **9** proved to be effective in the Strecker reaction of imines **7** with hydrogen

[*] Dr. L. Yet
Albany Molecular Research, Inc.
21 Corporate Circle, P.O. Box 15098
Albany, NY 12212-5098 (USA)
Fax: (+1) 518-257-2021
E-mail: larryy@albmolecular.com

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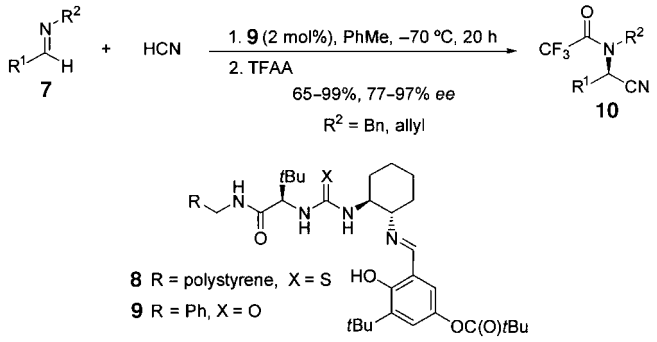
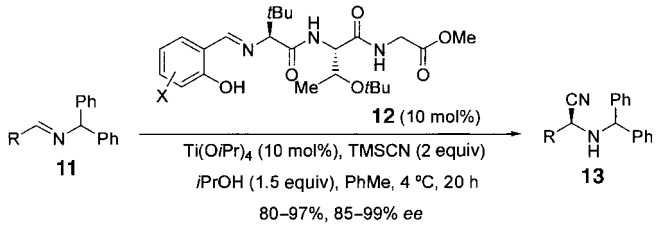
cyanide to afford trifluoroacetamides **10** after reaction with trifluoroacetic anhydride, since the free amines were not stable to chromatography (Scheme 4).[5]



Scheme 4. Asymmetric Strecker synthesis with salicylimine catalyst **9** (Vachal and Jacobsen). Bn = benzyl.

Catalyst **9** was very effective for the hydrocyanantion of both aromatic and aliphatic imines **7** in high enantioselectivities and yields, and either *N*-benzyl- or *N*-allylimines could be used. The key elements responsible for the high enantioselectivity were the presence of bulky *tert*-butyl substituents at both the amino acid position and at the 3-position of the salicylimine moiety. Resin-bound catalyst **8** allowed purification of the Strecker products by simple filtration and solvent removal, and the catalyst could be reused indefinitely without loss of either activity or enantioselectivity. Recently, Vachal and Jacobsen have applied catalyst **9** to ketoimines in the presence of hydrogen cyanide in the catalytic synthesis of quaternary α-carbon atoms.[6]

Snapper, Hoveyda and co-workers employed a similar salicylimine Schiff base ligand **12** in the asymmetric titanium-catalyzed Strecker reaction of aromatic *N*-benzhydrylimines **11** to give addition products **13** (Scheme 5).[7] It was found that

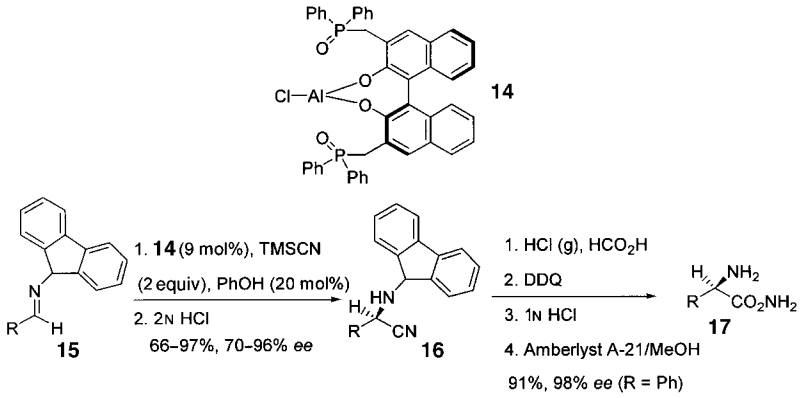


Scheme 5. Strecker synthesis with the chiral Schiff base ligand **12** (Snapper, Hoveyda, and co-workers). TMS = trimethylsilyl.

catalyst turnover was facilitated significantly in the presence of 2-propanol as an additive. The aminonitriles **13** are stable and directly purified by chromatography (acylation is not needed) and can be readily converted into the corresponding amino acids with 6 N HCl by concomitant cyanide hydrolysis and amine deprotection.

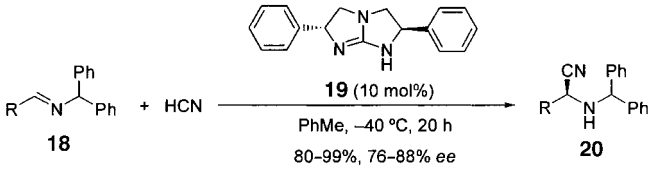
Shibasaki and co-workers disclosed a general asymmetric Strecker-type reaction that was controlled by bifunctional Lewis acid–Lewis base catalyst **14**.[8] *N*-Fluorenylimines **15** underwent catalytic asymmetric Strecker-type reactions with binaphthol catalyst **14** to give α-aminonitriles **16** in good to excellent enantioselectivities and yields (Scheme 6). α-Aminonitrile **16** (R = Ph) could then be converted into α-aminoamide **17** in several steps. Aromatic, aliphatic, heterocyclic, and α,β-unsaturated imines **15** were used as general substrates in these reactions. The origin of the highly enantioselective catalysis by **14** is believed to be attributed to the simultaneous activation of imines and trimethylsilyl cyanide by the Lewis acid and the oxygen atom of the phosphane oxide, respectively. With this catalyst system, *N*-allyl- and *N*-benzhydrylimines generally gave lower enantioselectivities. The addition of phenol was found to have a beneficial effect on the reaction rates.

Corey and Grogan recently developed a novel catalytic enantioselective Strecker reaction which utilized the readily



Scheme 6. Asymmetric Strecker synthesis with the bifunctional Lewis acid–Lewis base catalyst **14** (Shibasaki and co-workers). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

available chiral C_2-symmetric guanidine **19** as a bifunctional catalyst.[9] The addition of hydrogen cyanide to achiral aromatic and aliphatic *N*-benzhydrylimines **18** gave *N*-benzhydryl-α-aminonitriles **20** (Scheme 7), which were readily converted into the corresponding amino acids with 6 N HCl. The use of *N*-benzyl- or *N*-fluorenylimines afforded products of poor enantiomeric purity.



Scheme 7. Asymmetric Strecker synthesis with the chiral guanidine catalyst **19** (Corey and Grogan).

Kobayashi and co-workers employed the chiral zirconium binuclear catalyst **22** in the asymmetric Strecker-type synthesis of α-aminonitriles **23** from aldimines **21** with tributyltin cyanide (Scheme 8).[10] Aldimines **21** were in turn derived from aliphatic, aromatic, and heterocyclic aldehydes. High levels of enantioselectivities were observed in these reactions.

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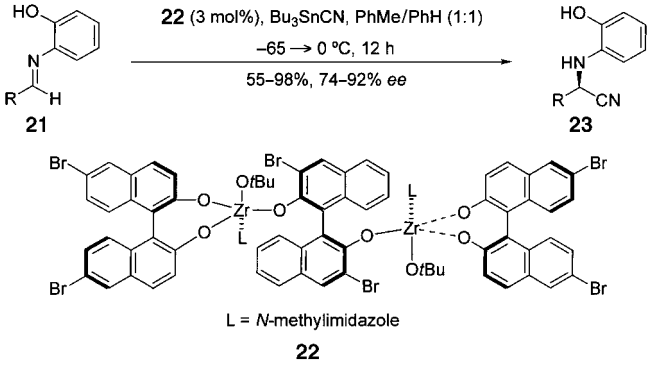
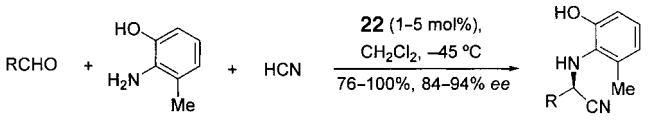


Scheme 8. Asymmetric Strecker synthesis with the chiral zirconium binuclear catalyst **22** (Kobayashi and co-workers).

These α-aminonitriles could be converted into α-amino acid derivatives by methylation of the phenolic hydroxyl group, followed by acid or base hydrolysis and oxidative cleavage with cerium ammonium nitrate. Furthermore, the catalytic asymmetric Strecker amino acid synthesis starting from achiral aldehydes, amines, and hydrogen cyanide using catalyst **22** has been achieved (Scheme 9). It is noted that



Scheme 9. Three-component Strecker synthesis with the chiral zirconium binuclear catalyst **22** (Kobayashi and co-workers).

150 years after the first discovery of the Strecker reaction, a truly efficient three-component asymmetric version has been accomplished.[10b] While the use of tributyltin cyanide is suitable for laboratory-scale experiments, industrial applications are expected for a more benign three-component catalytic asymmetric Strecker process using hydrogen cyanide.

This Highlight has shown that catalytic asymmetric Strecker-type reactions are possible but are still under active investigation for improvements and generalizations. Important areas for future study will include wider application of starting aldimine substrates, finer catalyst tuning, and of the simple conversion of α-aminonitriles into α-amino acid derivatives. More importantly, large-scale industrial applications of these methods to the production of optically active α-amino acids will be the ultimate goal of these investigations.

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