Catalytic Enantioselective Strecker Reactions and Analogous Syntheses

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1. Introduction

The Strecker reaction which was reported already in 1850 is the oldest known synthesis of α-amino acids.[1] This reaction comprises a condensation of an aldehyde, ammonia, and cyanide source, followed by subsequent hydrolysis of the resulting α-amino nitrile (Scheme 1; route a). In addition, the Strecker reaction represents one of the simplest and most economical methods for the preparation of α-amino acids[2] on lab scale as well on a technical scale. Furthermore, the substrates are very cheap and available in commercial quantities. In industry, the Strecker reaction is applied widely due to those economically favorable properties.

When using amines instead of ammonia, the preformation of imines, followed by hydrocyanation (Scheme 1; route b) instead of the one-pot synthesis represents a popular and widely used alternative route. The imines can be easily obtained starting from an aldehyde and an amine component.

There has also been considerable interest to extend this reaction toward an asymmetric process for the production of optically active α-amino acids, in particular, nonproteinogenic α-amino acids. The importance of the latter products is rapidly increasing since they are often used as key building blocks in pharmaceuticals, and several approaches, comprising, e.g., biocatalytic routes[3] as well as the asymmetric metal-catalyzed hydrogenation of enamides,[4] have already

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Harald Gröger, born in 1968 in Erlangen (Germany), studied chemistry at the Universities of Erlangen-Nürnberg and Oldenburg. He received his doctorate (Dr. rer. nat.) at the University of Oldenburg under the direction of Professor Jürgen Martens in 1997. From 1997 to 1998, he was a JST postdoctoral fellow in the group of Professor Masakatsu Shibasaki at the University of Tokyo, working on enantioselective syntheses with heterobimetallic catalysts. In 1998, he joined the R&D department of the speciality and fine chemicals division at SKW Trostberg AG. After the merger between SKW Trostberg AG and Degussa-Hüls AG in 2001, he became a project manager in the Project House Biotechnology of the new Degussa AG. Currently, he is focusing on the development of industrially feasible biocatalytic processes. His research interests include all aspects of catalysis by means of biocatalysts and synthetic catalysts, as well as the chemistry of heterocycles. He has authored 40 publications, and several patent applications.

been developed. Nevertheless, there is still a need for further efficient and, in particular, technically feasible methods in this field. The above-mentioned advantages of the Strecker reaction have attracted many chemists to focus on the design of suitable asymmetric versions of this efficient α-amino acid synthesis. In particular, asymmetric catalytic processes are desirable.[5] Although unknown until the middle of the 1990s, several successful achievements in catalytic asymmetric Strecker reactions were reported by different groups within the past few years.[6,7] A popular asymmetric concept is based on the use of preformed imines and a subsequent nucleophilic addition of HCN or TMSCN in the presence of a chiral catalyst (Scheme 2; routes a and b). However, also a one pot-type catalytic asymmetric Strecker synthesis has been developed successfully (Scheme 2; route c). It is noteworthy that the range of suitable catalysts is broad, covering organocatalysts (Scheme 2; route a) as well as metal catalysts (Scheme 2; routes b and c). In addition, related reactions analogous to the Strecker reaction leading to comparable products have also been developed (Scheme 2; routes d and e). These approaches are based on the use of either another donor instead of cyanide (which, however, also represents a carboxylic acid synthon) or an iminium system (instead of an imine). A graphical overview of the catalytic concepts of the asymmetric Strecker reactions and analogous syntheses is given in Scheme 2.

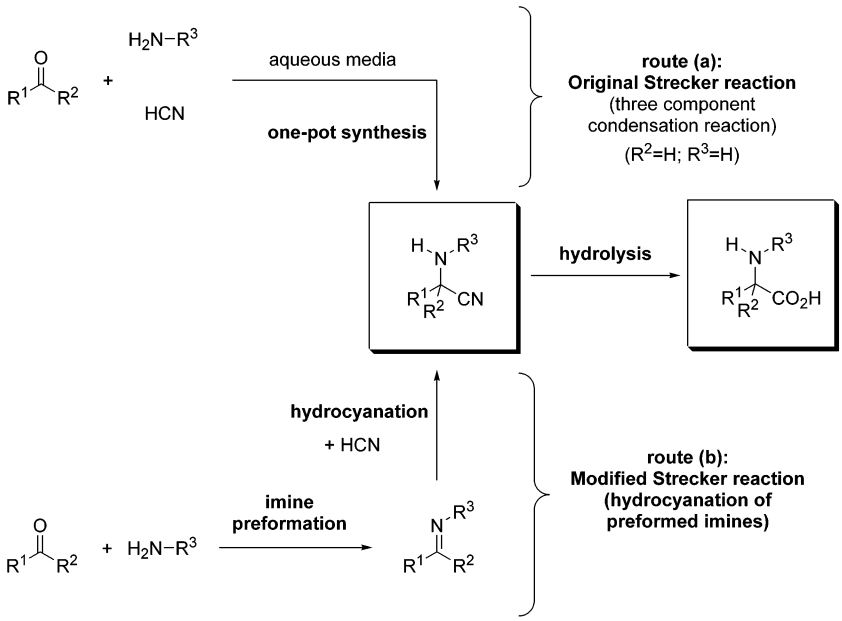
The following review will summarize the achievements in the field of catalytic asymmetric Strecker reactions. Related syntheses according to Scheme 2 which also start from imines to give α-amino acids, will be described briefly, too, albeit they do not represent "typical" Strecker reactions.

2. Enantioselective Strecker Reaction Using Organocatalysts

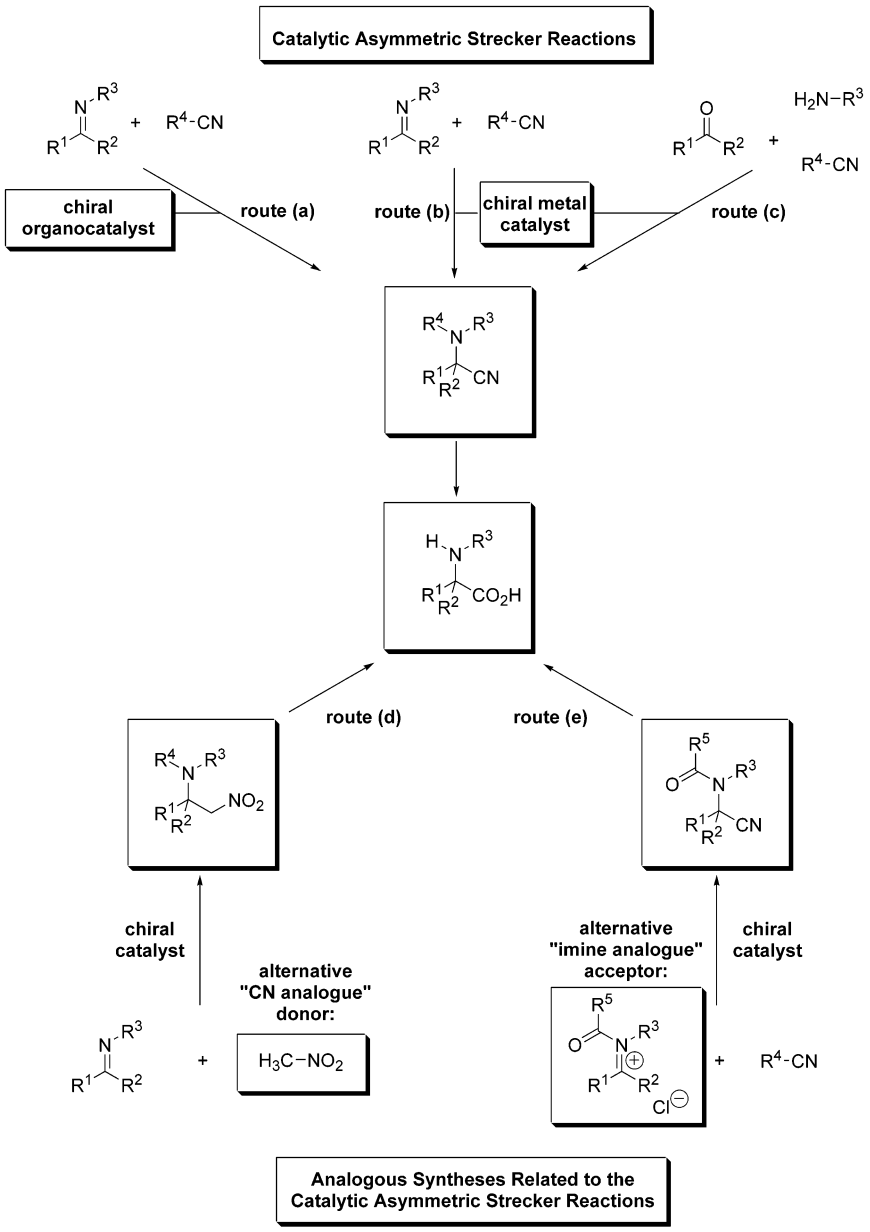
2.1. Overview

In addition to metal-catalyzed asymmetric cyanations (which will be described in section 3), several versions of this process based on the use of organocatalysts have been developed so far. Interestingly, completely different types of organic molecules were found to possess catalytic hydrocyanation properties. A summary of these organocatalysts which comprises a chiral diketopiperazine,[8,9] a bicyclic guandidine,[10] and imine-containing urea derivatives[11−16] is given in Scheme 3. A joint characteristic of all those molecules is the presence of an imino bond moiety which appears to be beneficial for catalyzing the hydrocyanation process. The imino bond might be

Scheme 1. Principles of Different Types of Strecker Reactions



Scheme 2. Overview of Catalytic Asymmetric Strecker Reactions and Analogous Syntheses



incorporated into a guanidine framework, but also imines derived from salicylaldehyde work well as highly efficient asymmetric catalysts. Very recently, a chiral *N*-oxide was found which promotes the cyanosilylation of aldimines.[17] However, in this case, stoichiometric amounts are (still) required.

2.2. Chiral Diketopiperazines as a Catalyst

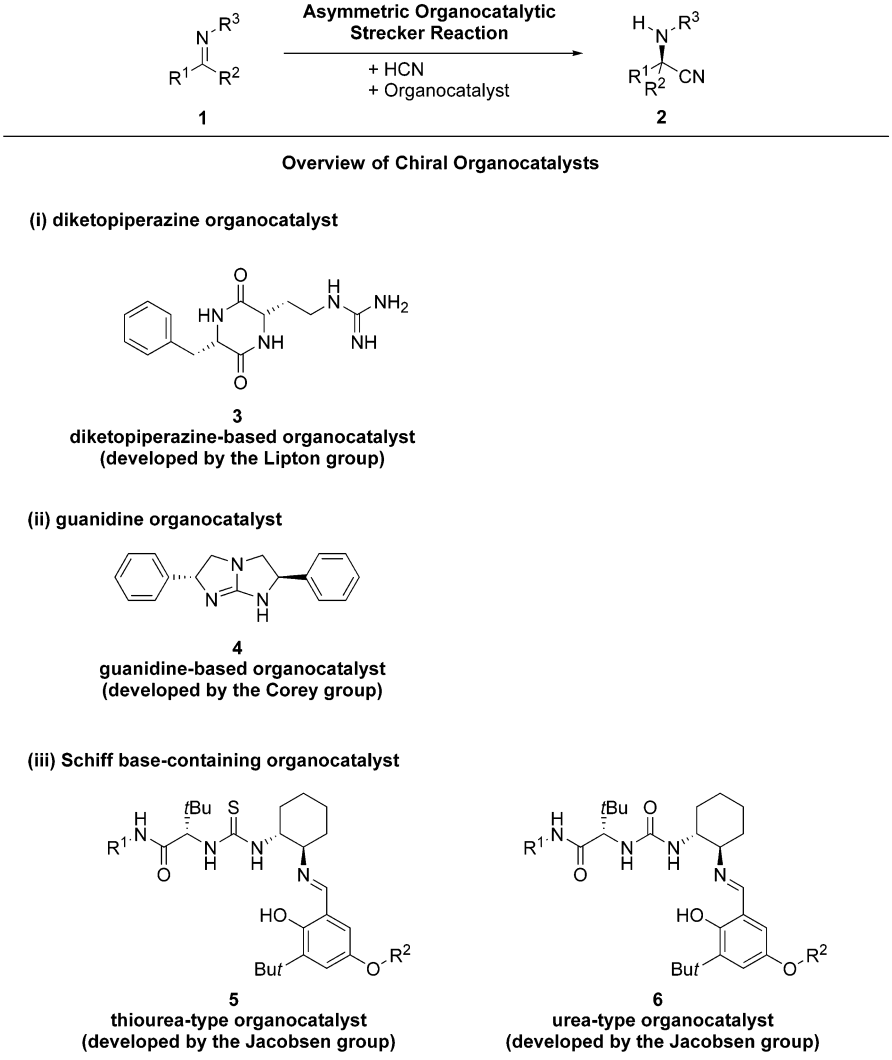
2.2.1. The Catalytic Concept

The first asymmetric catalytic version of a Strecker amino acid synthesis has been reported by the Lipton group in 1996.[8,9,18] The catalytic concept is based on the application of a cyclic dipeptide, **3**, as a catalyst. Diketopiperazines were chosen due to the success of those molecules as efficient organocatalysts in the previously developed hydrocyanation of aldehydes.[19,20] However, when using the diketopiperazine **7** (Scheme 4) as the most effective catalyst in the cyanohydrin synthesis, an asymmetric induction in the Strecker reaction was not observed.

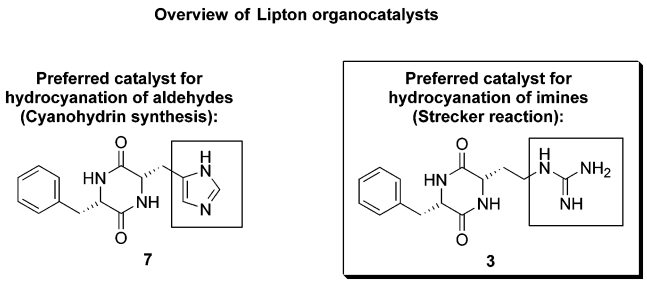
This nonsatisfactory result was explained by the failure of the imidazole side chain to accelerate the proton transfer of HCN in the Strecker reaction. As a consequence, a more basic side chain was expected to give better results. The breakthrough was achieved when replacing the imidazole moiety by a guanidine moiety, which turned out to be a prerequisite for a high asymmetric induction in the asymmetric Strecker reaction.[8,9] This diketopiperazine **3** is accessible by means of a multistep synthesis starting from (*S*)-phenylalanine and (*S*)-α-amino-γ-guanidinobutyric acid. In the presence of a catalytic amount of only 2 mol %, the hydrocyanation of *N*-benzhydryl imine **8a** proceeds at −25 °C under formation of the amino nitrile (*S*)-**9a** in 97% yield, and with an excellent enantioselectivity of >99% ee (Scheme 5).

It is noteworthy that a highly enantioselective reaction was also observed when using several other

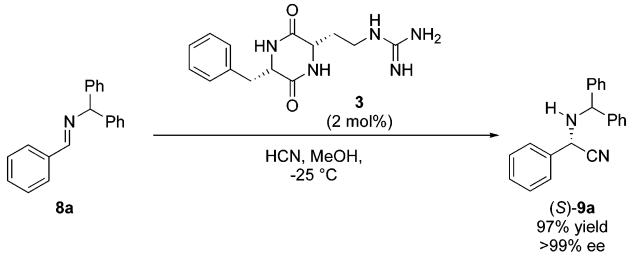
Scheme 3. Overview of Organocatalysts



Scheme 4. Chiral Diketopiperazine Organocatalysts



Scheme 5. Lipton-Type Strecker Reaction



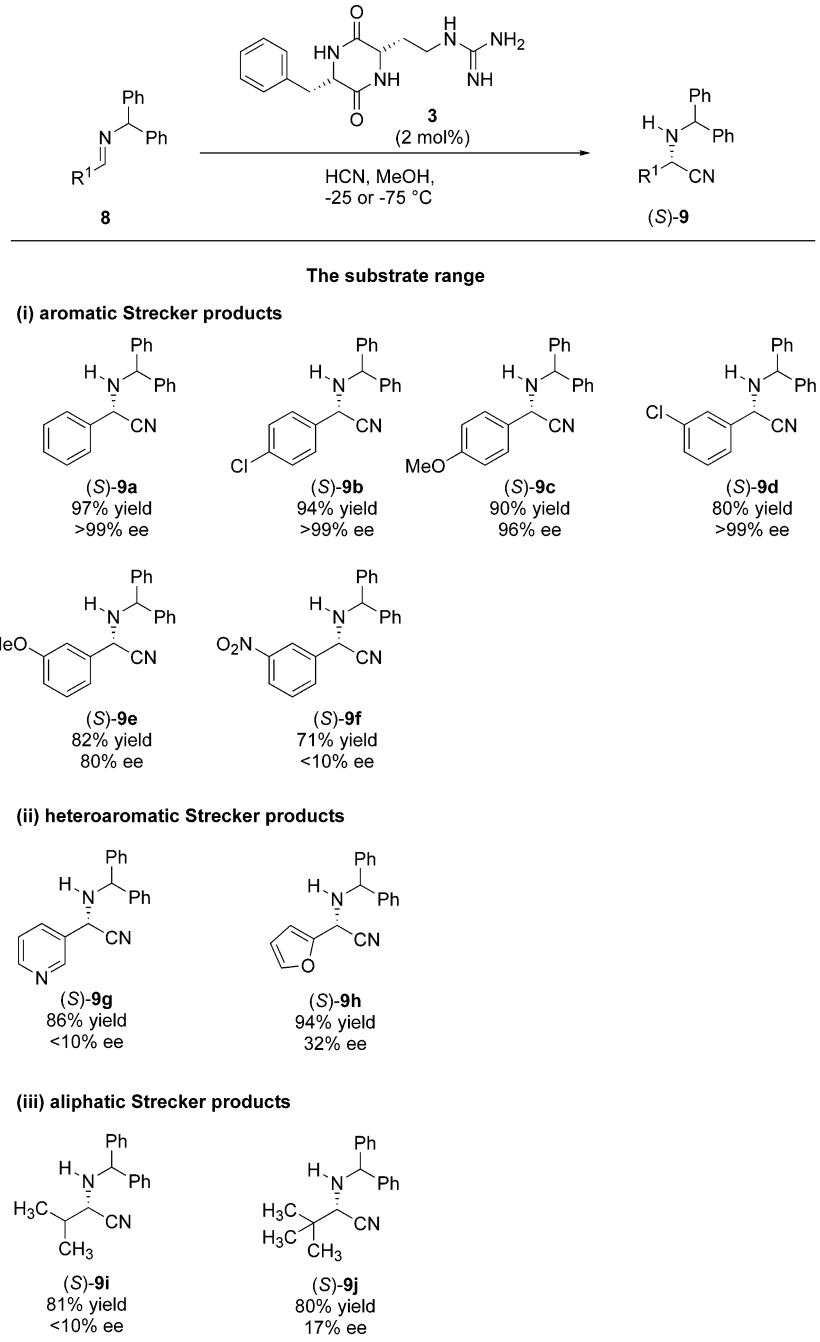
types of benzaldimines with substituted benzyl groups as an *N*-substituent. However, a moderate enantioselectivity of only 75% ee was obtained with the corresponding imine bearing an *N*-Boc substituent.

2.2.2. The Substrate Range

The cyclic dipeptide represents not only the first catalyst for the asymmetric Strecker reaction, but still belongs to the most efficient ones. This is underlined by the investigation of the substrate range of this organocatalytic asymmetric Strecker reaction. The reaction which is carried out at a low catalytic amount of 2 mol % of **3** was studied intensively with a broad variety of *N*-benzhydryl-substituted imines, and led to the corresponding (*S*)-enantiomers, (*S*)-**9**.[8] Despite exceptions (e.g., product (*S*)-**9f**), good to excellent enantioselectivities of 80−99% ee were obtained generally when starting from imines derived from benzaldehyde or electron-deficient aromatic aldehydes. For example, the 3-chloro-substituted benzaldimine **8d** led to the formation of the corresponding α-amino nitrile (*S*)-**9d** in 80% yield and with >99% ee. The analogous 4-chloro-substituted product (*S*)-**9b** was formed in 94% yield, and with >99% ee. Increasing the reaction temperature to −25°C, however, led to a remarkably decreased enantioselectivity of 64% in this case.

In contrast to electron-deficient aromatic imines, heteroatom-substituted aromatic imines gave considerably lower enantioselectivities. For example, 2-furyl- and 3-pyridyl-containing imines led to the

Scheme 6. Substrate Range of the Lipton-Type Strecker Reaction



products (*S*)-**9g** and (*S*)-**9h** with <10% ee and 32% ee, respectively. In contrast to the high efficiency for aromatic substrates, the organocatalyst **3** does not appear to be suitable for hydrocyanations of imines derived from alkyl-substituted aldehydes. Starting from the aliphatic aldimines **8i** and **8j**, respectively, only poor enantioselectivities of 17% ee or less were obtained for the products (*S*)-**9i**, and (*S*)-**9j**. An overview of the substrate range is given in Scheme 6.[8]

Although the reaction shows a broad generality, the catalytic abilities of the dipeptide were very sensitive toward various parameters such as solvent viscosity, and the crystallization method of the catalyst. The latter reason is interesting in particular since **3** does not act as a heterogeneous catalyst but is soluble under the reaction conditions.

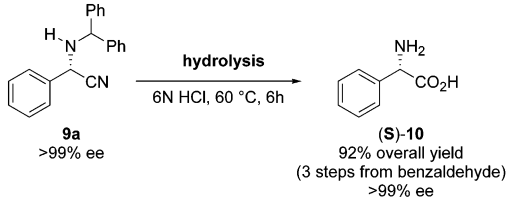
A *direct* Strecker reaction starting from benzaldehyde, ammonia, and hydrocyanide has also been tried using the organocatalyst **3**.[8] However, although the Strecker product was formed, it turned out that the product was racemic. In addition, it turned out that *N*-substituted imines are better substrates due to a higher stability of the resulting α-amino nitriles.

2.2.3. Transformation of the Amino Nitriles into α-Amino Acids

The *N*-substituted α-amino nitriles, in particular, when bearing an *N*-benzhydryl substituent, can be converted in one step into the corresponding α-amino acids without loss of enantiomeric excess. For example, (*S*)-phenylglycine, (*S*)-**10**, was obtained from the optically active *N*-benzhydryl aldimine **8a** in enantiomerically pure form. Thus, starting from

benzaldehyde, the desired α-amino acid (*S*)-phenylglycine, (*S*)-**10**, was obtained in 92% overall yield (for the three steps imine formation, Strecker synthesis, and hydrolysis) and with >99% ee (Scheme 7).[8] These data underline the high efficiency of this concept for an α-amino acid synthesis developed by Lipton et al., which contains an organocatalytic Strecker reaction as a key step.

Scheme 7. Synthesis of (*S*)-Amino Acids

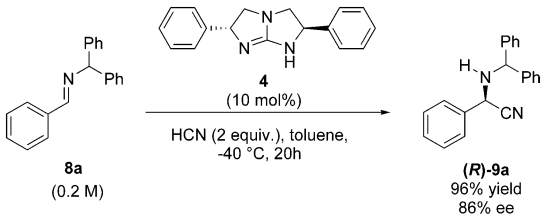


2.3 Chiral Guanidines as a Catalyst

2.3.1. The Catalytic Concept

The ability of a further, but completely different, type of guanidine to act as an efficient catalyst in the asymmetric addition of hydrogen cyanide to imines was reported by the Corey group.[10] This C_2-symmetric catalyst, **4**, is readily available in a multistep synthesis starting from D-phenylglycine, which represents a cheap and easily accessible chiral starting material. In the presence of 10 mol % of **4**, which has a guanidine functionality embedded in a bicyclic framework, the addition of HCN to *N*-benzhydryl imines has been investigated in detail. The hydrocyanation of the benzaldehyde-derived imine, **8a**, gave the corresponding (*R*)-amino nitrile (*R*)-**9a** in 96% yield, and with an enantioselectivity of 86% ee (Scheme 8).[10] The reaction can be also carried out at an increased reaction temperature of −20°C, which results in a faster reaction rate (99% yield after 8 h) and comparable 82% ee.

Scheme 8. Corey-Type Strecker Reaction



Additionally, it turns out that the choice of the *N*-substituent is of importance. In contrast to the high enantioselectivities when using an imine bearing a *N*-benzhydryl substituent, remarkably lower asymmetric induction was observed for other types of *N*-substituents. For example, *N*-benzyl- or *N*-(9-fluorenyl)-substituted imine substrates gave low enantioselectivities of 0−25% ee.

2.3.2. The Substrate Range

The hydrocyanation using the Corey catalyst, **4**, has been investigated toward its substrate range with a broad variety of aromatic and aliphatic imines **8** bearing an *N*-benzhydryl substituent. This Strecker reaction which is typically carried out with a catalytic amount of 10 mol % of **4** was shown to be very general for a broad range of substituted aromatic imines. Selected examples are shown in Scheme 9. When using imines resulting from benzhydrylamine and an aromatic aldehyde, the amino nitriles of type (*R*)-**9** were obtained in excellent yields of 80−99%, and enantioselectivities of up to 88% ee.[10] For example, the 4-methoxy-substituted benzaldimine, **8c**, led to the formation of the corresponding product (*R*)-**9c** in excellent yield of 99%, and with 84% ee. In general, the enantioselectivity appears to be independent of the type of substituent in the 4-position, since a broad variety of 4-substituted benzaldimines gave the corresponding α-amino nitriles with similar high enantioselectivities in the range of 80−88% ee.

The *o*-methyl substituted benzaldimine led to the product **9o** with a somewhat lower enantioselectivity of 50% ee. Compared to the diketopiperazine-catalyzed hydrocyanation described above, aromatic substrates gave slightly lower enantioselectivities. However, it is noteworthy that in contrast to the diketopiperazine-catalyzed hydrocyanation, the use of aliphatic aldimines as a substrate led to good results with high yields of ca. 95%, and enantioselectivities in the range of 63−84% ee as has been shown for the synthesis of the α-amino nitriles (*S*)-**9j**, (*S*)-**9p**, and (*S*)-**9q** (Scheme 9).[10]

For example, the α-amino nitrile (*S*)-**9j**, which represents a precursor for the pharmaceutically important L-*tert*-leucine,[21] has been obtained in ca. 95% yield, and with 84% ee.[10]

It is noteworthy that (*S*)-enantiomers are obtained when using aliphatic imines, which represents the opposite absolute configuration compared to the aromatic α-amino nitriles. This effect has been mechanistically explained by the Corey group in detail (for the reaction mechanism in general, see also the mechanistic section below). It is also noteworthy that the catalyst **4** can be recovered for reuse in 80−90% yield by extraction with oxalic acid.

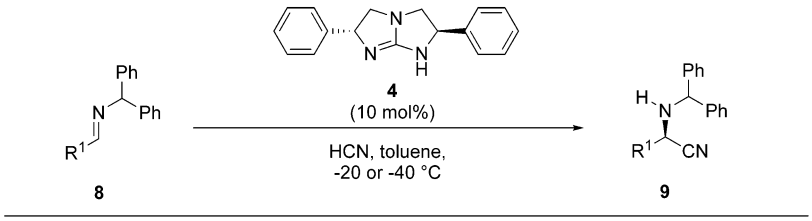
2.3.3. The Transformation of Amino Nitriles into α-Amino Acids

The α-amino nitrile products of type **9** were easily transformed into the corresponding α-amino acids group via hydrolysis in HCl. Thus, in one step the benzhydryl group is removed, and the cyano group is hydrolyzed.

2.3.4. The Reaction Mechanism

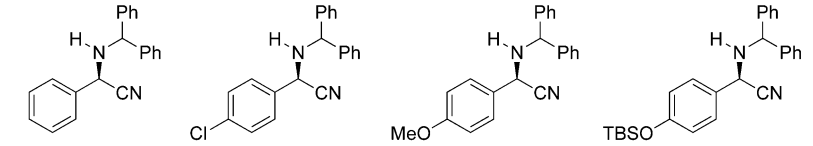
From a mechanistic point of view, it is interesting that the *N*-methylated catalyst is inactive, indicating the mechanistic importance of the hydrogen atom (attached to the nitrogen) by binding the nitrogen of the imine bond in the transition state.[10] In a first step, a guanidinium cyanide complex, **11**, is formed, followed by the generation of a complex, **12**, bearing the above-mentioned hydrogen bond with the aldimine, e.g., **8a**. The subsequent addition of the cyanide ion within the ion pair **12** then furnishes the Strecker product, **9a**, with high enantioselectivity. The catalytic cycle proposed by the Corey group is shown in Scheme 10, representatively for the hydrocyanation

Scheme 9. The Substrate Range of the Corey-Type Strecker Reaction



The substrate range (selected examples)

(i) aromatic Strecker products

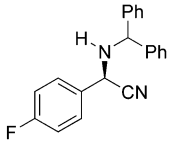


(*R*)-**9a** 96% yield 86% ee

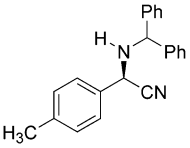
(*R*)-**9b** 88% yield 81% ee

(*R*)-**9c** 99% yield 84% ee

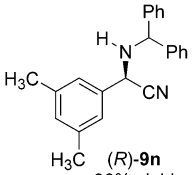
(*R*)-**9k** 98% yield 88% ee



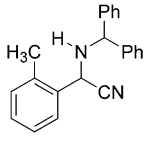
(*R*)-**9l** 97% yield 86% ee



(*R*)-**9m** 96% yield 80% ee

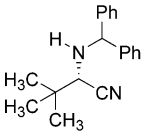


(*R*)-**9n** 96% yield 79% ee

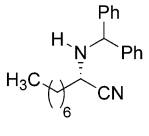


9o 88% yield 50% ee

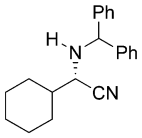
(ii) aliphatic Strecker products



(*S*)-**9j** ~95% yield 84% ee

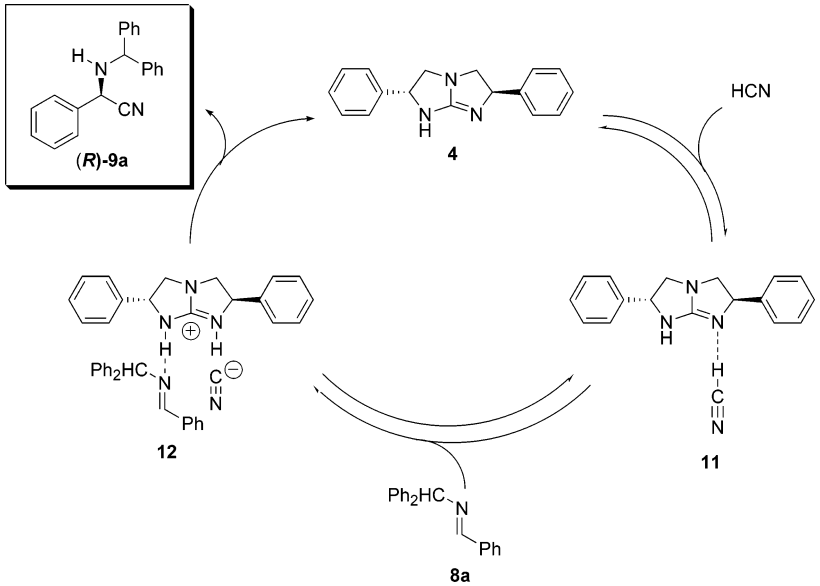


(*S*)-**9p** ~95% yield 63% ee



(*S*)-**9q** ~95% yield 76% ee

Scheme 10. The Reaction Mechanism



of imine **8a**.[10] In addition, this catalytic cycle gave an insight with respect to the origin of the enantioselectivity. On the basis of the modeling of pre-transition state assemblies,[10] the Corey group found an explanation for the opposite absolute configurations obtained for aromatic and aliphatic Strecker

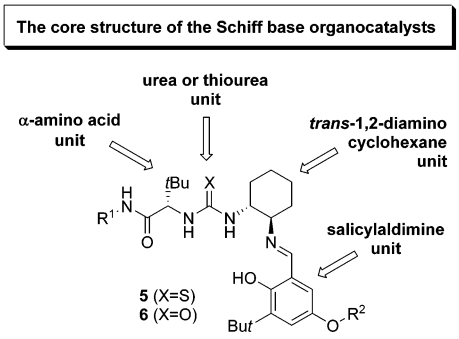
products, respectively. Furthermore, this successful modeling study,[10] which is based on van der Waals attractive interactions involving nonpolar groups as a source of three-dimensional ordering in the transition state, underlines that modeling represents an efficient tool to clarify reaction mechanisms and stereoselectivity issues of asymmetric catalytic processes.

2.4. Chiral Imine-Containing Urea Derivatives as a Catalyst

2.4.1. The Catalytic Concept

Another type of organocatalyst highly suitable for an asymmetric cyanide addition reaction to the C═N double bond are chiral urea or thiourea derivatives of type **5** or **6**, bearing an imine bond (Scheme 11).[11−16] These organocatalysts which turn out to be highly efficient have been developed by the Jacobsen group. The core structure, and characteristic structural components thereof, are shown in Scheme 11. As a chiral precursor for the preparation of this catalyst, enantiomerically pure 1,2-cyclohexyldiamine was used in addition to an optically active alkyl α-amino acid, preferrably L-*tert*-leucine. These new types of organocatalysts **5**,**6** were found via high throughput screening (HTS) of resin-bound derivatives.[11−13,22] Due to several units in the catalyst, e.g., diamine, and α-amino acid, a broad systematic structure variation is possible leading to a high diversity of potential catalysts.[11−13]

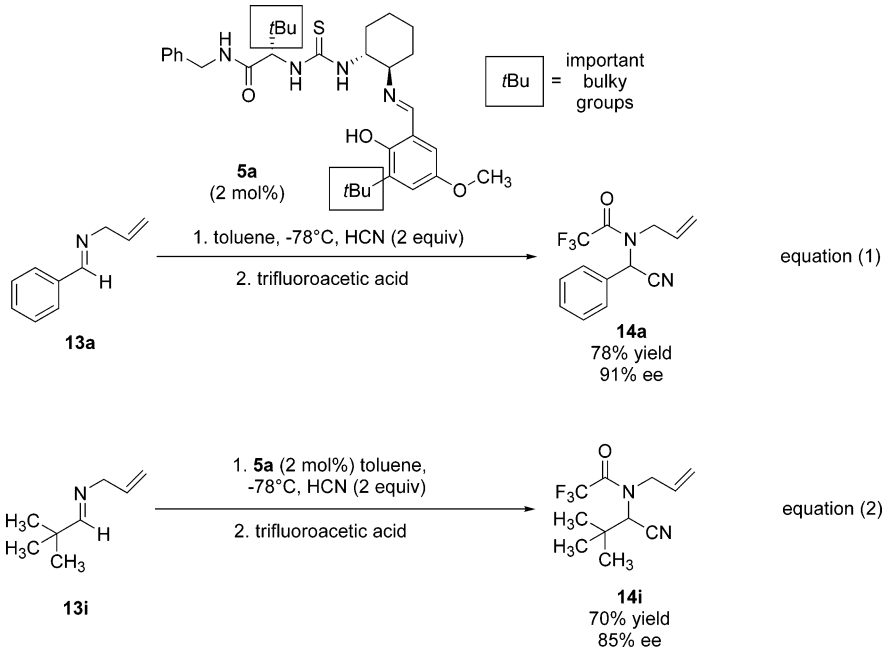
Scheme 11. Core Structure of Schiff Base Organocatalysts for the Strecker Reaction



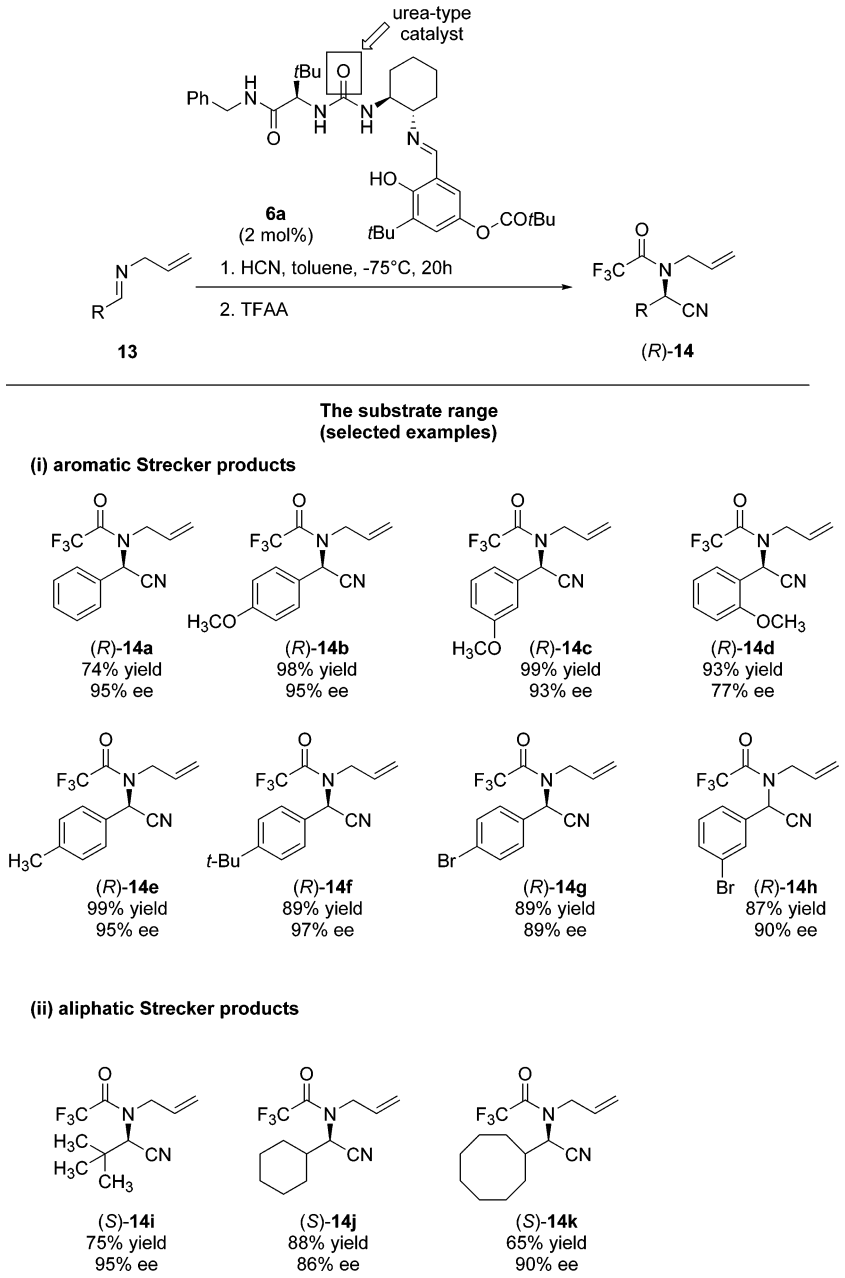
The HTS-optimization of the hydrocyanation was carried out in three stages with three libraries consisting of 12, 48, and 132 members, respectively.[11] From an initial lead result of 19% ee, this iterative optimization led to an enantioselectivity of 91% ee. In the first screening stage, the initially used Schiff base was applied in the model reaction in the absence and presence of metal ions showing that the best enantioselectivity was observed in the absence of a metal. Subsequent variation of the diamine and the α-amino acid units as well as the substitution pattern at the salicylaldimine and the use of a thiourea functionality led to the optimized catalyst **5a**. In the presence of a catalytic amount of 2 mol %, the Strecker synthesis at −78 °C with *N*-allyl benzaldimine, **13a**, gave the α-amino nitrile **14a** in 78% yield, and with high 91% ee (Scheme 12; eq 1).[11]

Some other imines were also tested, but gave slightly lower enantioselectivities in the range of 70−88% ee. For example, for the formation of the *tert*-leucine precursor **14b**, 70% yield, and an enantioselectivity of 85% ee was observed (Scheme 12; eq 2).[11] On the basis of this promising organocatalyst **5a**, a subsequent second screening was done with the aliphatic imine **13i** as a substrate, revealing a polymer-supported thiourea derivative of the 5-pivaloyl-substituted Schiff-base **6a** as the superior catalyst.[14] For further intensive studies with respect to scope and limitations, **6a** was used directly in the nonimmobilized form (the urea derivative **6a** was chosen instead of the analogue thiourea compound due to an easier preparation, and comparable results which were obtained).

Scheme 12. Jacobsen-Type Strecker Reaction



Scheme 13. The Substrate Range of the Jacobsen-Type Strecker Reaction



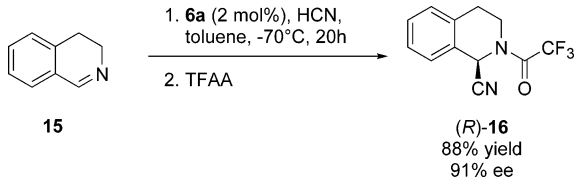
2.4.2. The Substrate Range /1: Amino Nitriles Derived from Aldimines

This optimized soluble urea catalyst, **6a**, gave good to high enantioselectivities with aromatic imines bearing an *N*-allyl substituent.[14] In the presence of the soluble urea catalyst **6a**, yields of up to 74−99%, and enantioselectivities of 77−97% ee were obtained for the corresponding aromatic α-amino nitriles, (*R*)-**14** (Scheme 13). For the hydrocyanation of *N*-allyl benzaldimine, a yield of 74%, and an improved enantioselectivity of 95% ee were found for the product (*R*)-**14a** compared with 91% in case of catalyst **5a**. Notably, higher yields of at least 87% were obtained for substituted *N*-allyl benzaldimines, (*R*)-**14b**−**h**. Excellent results were also obtained for those products with respect to enantioselectivity. For example, the aromatic α-amino nitrile (*R*)-**14f** containing a bulky *tert*-butyl-substituent was formed in 89% yield, and with 97% ee.[14]

In addition, acyclic aliphatic *N*-allyl imines as well as cycloalkylimines were accepted as a starting material for the asymmetric hydrocyanation with enantioselectivities of up to 95% ee with **6a** as catalyst.[14] It is noteworthy, in particular, that the use of the bulkyl imine **13i** bearing a *tert*-butyl substituent gave the Strecker adduct (*R*)-**14i** in 88% yield and with 95% ee. This compound is a precursor for the preparation of the nonproteinogenic amino acid D-*tert*-leucine, which is an interesting chiral building block. Further representative examples of the substrate range are summarized in Scheme 13. It also turns out that the analogous *N*-benzyl imines can be used without significant difference compared with the *N*-allyl imines.[14]

Furthermore, this Jacobsen-type hydrocyanation is also applicable for cyclic imines,[14] as has been demonstrated in the efficient synthesis of (*R*)-**16** in 88% yield and with 91% ee (Scheme 14). Thus, in

Scheme 14. Strecker Reaction with Cyclic Imines

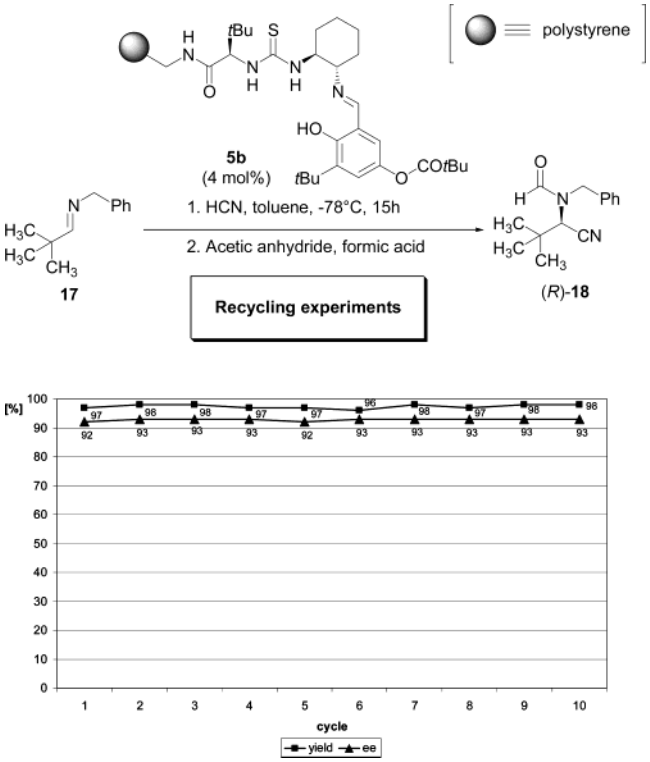


addition to the hydrocyanation of acyclic imines which are (mainly) *E* isomers, *Z*-imines also can be used efficiently. Notably, the same sense of stereoinduction was observed with respect to the benzylic center atom.

2.4.3. Process Development Studies and Catalyst Improvement

An interesting process development study was carried out by the Jacobsen group for the synthesis of the aliphatic α-amino nitrile (*R*)-**18**, showing that recycling of the resin-bound catalyst, **5b**, can be successfully done.[14] At first, a comparison of the soluble urea catalyst, **6a**,[23] and the polymer-supported thiourea analogue, **5b**, showed that both organocatalysts gave similiar enantioselectivities (95 vs 91% ee). Albeit ee is ca. 2−4% lower for the latter one, this catalyst **5b** is more suitable for recycling studies due to its easy separation from the reaction mixture. Using this polymer-supported catalyst **5b** in the hydrocyanation of imine **17** revealed that it can be reused very efficiently maintaining high yields of 96−98%, and enantioselectivities of 92−93% ee over (at least) 10 reaction cycles (Scheme 15).[14]

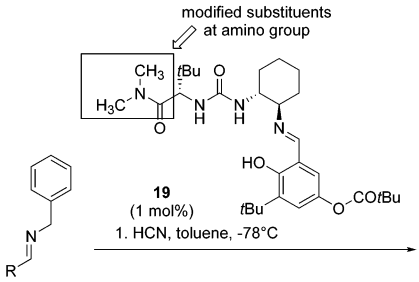
Scheme 15. Recycling Studies Using Chiral Schiff-Base Organocatalyst



Those hydrocyanation reactions were carried out at −78°C with a catalytic amount of only 4 mol %. The formed α-amino nitriles were converted in situ into the corresponding *N*-formyl derivatives, which were subsequently isolated.

On the basis of an impressive rational "mechanism-driven" optimization (for this mechanistic study,[16] see the corresponding section below), a further improved catalyst **19** was found very recently. This new catalyst, which is superior to **5a** and **6a**, turned out to be the most enantioselective Strecker catalyst prepared to date.[16] When using aliphatic as well as aromatic aldimines in the presence of 1 mol % of **19**, excellent enantioselectivities in the range of 96−99.3% ee were obtained. An overview about the resulting enantioselectivities, and a comparison with the ee values obtained in the presence of catalyst **6a**, are given in Scheme 16.

Scheme 16. Optimized Jacobsen-Type Organocatalyst



R	ee [%]
Ph	99.3 (96)
i-Pr	97 (80)
t-Bu	99.3 (96)
n-Pent	96 (79)

a) For comparison, in parentheses the ee values obtained in the presence of catalyst **6a** is given.

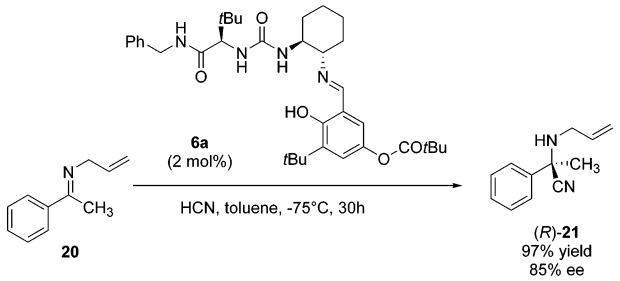
2.4.4. Strecker Reaction using Ketimines

In addition to aldimines, the imine-based organocatalysts also efficiently catalyze the hydrocyanation of ketimines leading to α-amino nitriles of type **21** or **23** bearing a stereogenic quaternary carbon center.[15] It should be added that this work by the Jacobsen group represents the first example of a highly enantioselective hydrocyanation of ketimines. These type of α-amino nitriles are suitable precursors for the synthesis of α-quaternary α-amino acids, which are used as intermediates for the synthesis of a broad variety of pharmaceutically important compounds.[24−26] So far, those compounds have been manufactured by biocatalytic methods mainly.[27]

Although the resin-bound catalyst **5b** which is efficient for the hydrocyanation of aldimines was also found to be useful for ketimines, long reaction times of 180 h were required to obtained the product (*R*)-**21** in 95% yield, and with 85% ee.[15] A remarkable increase of the reaction rate has been achieved when using urea catalysts **6**. The highest reactivity was found in the presence of the soluble catalyst **6a** (2 mol %) with a high yield of 97 and 85% ee within 30 h (Scheme 17).

N-substituent allyl or benzyl groups were used due to their easy subsequent cleavage from the amino-

Scheme 17. Strecker Reaction Using Ketimines



alkylated products. However, *N*-allyl-substituted aminonitriles were found to be unstable under acidic or basic conditions, whereas Strecker adducts with an *N*-benzyl group are more stable, and additionally led to slightly improved enantioselectivities. Thus, the *N*-benzyl substituted imines of type **22** have been used for the subsequent detailed investigation of the substrate range (Scheme 18).[15] It was further shown that there is only a little influence of substituents at the *N*-benzyl group on enantioselectivity. It should also be added that the catalyst **6a** can be easily recovered by chromatography with 97% recovery yield, and successfully reused.

2.4.5. The Substrate Range /2: Amino Nitriles Derived from Ketimines

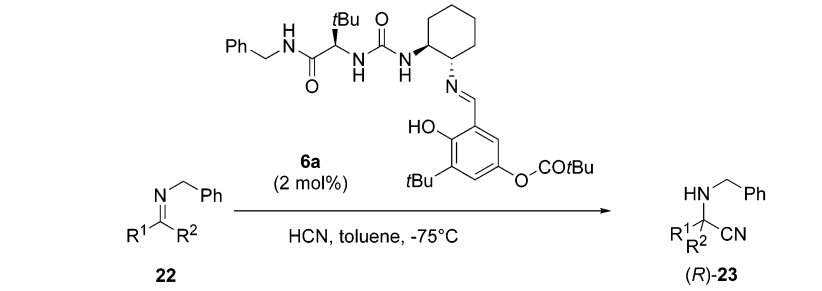
In general, high enantioselectivities of 88−95% ee were obtained with a broad variety of *N*-benzylated aromatic substrates **22** as shown in Scheme 18.[15] An exception are *o*-substituted ketimines. For the *o*-bromo substituted aromatic ketimine, **22h**, the resulting product, (*R*)-**23h**, was formed with 45% (due to decomposition problems) and only 42% ee. The use of *N*-benzyl *tert*-butylmethylimine, **22i**, as a selected aliphatic imine led to the Strecker adduct (*R*)-**23i** in 98% yield, and with 70% ee, demonstrating the suitability of this method also for aliphatic substrates (Scheme 18).

Since some of the Strecker adducts were obtained as crystalline compounds, recrystallization furnished enantiomerically pure products with impressive >99.9% ee, and 75−79% overall isolated yields (e.g., in case of (*R*)-**23c** and (*R*)-**23e**,**f**).

2.4.6. Transformation of the Amino Nitriles into α-Amino Acids

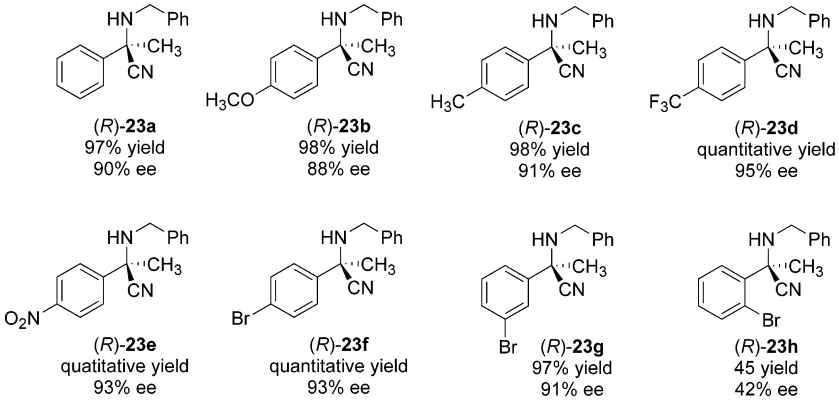
A further key feature of the Strecker reaction concept of the Jacobsen group is the simple trans-

Scheme 18. Substrate Range of the Strecker-Type Reaction Using Ketimines

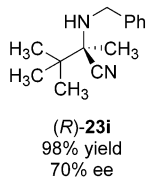


The substrate range

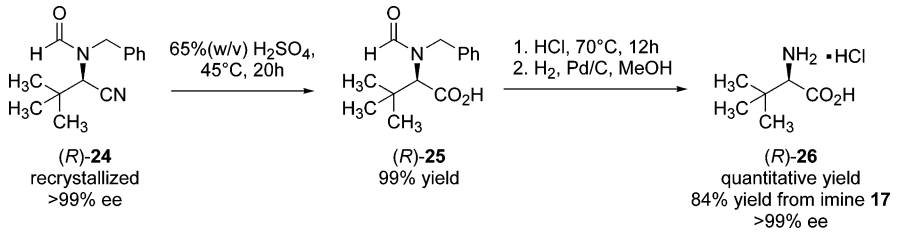
(i) aromatic Strecker products



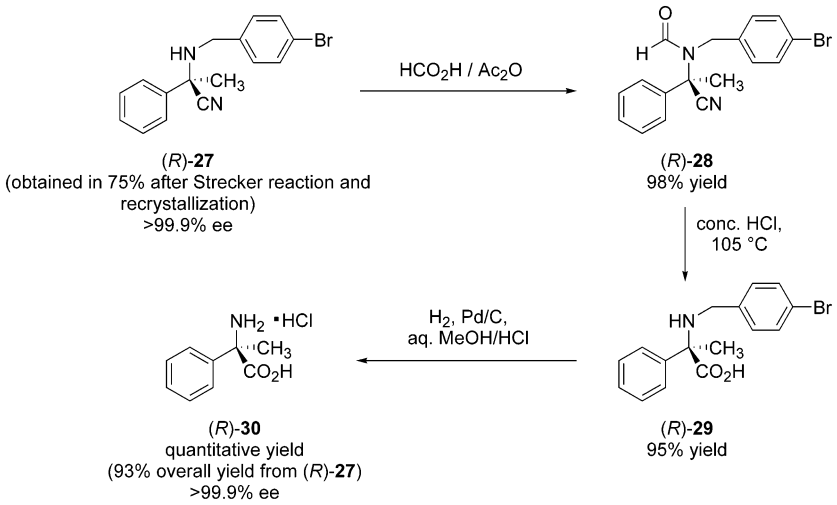
(ii) aliphatic Strecker products



Scheme 19. Synthesis of (*R*)-*tert*-Leucine Hydrochloride



Scheme 20. Synthesis of (*R*)-α-Methylphenylglycine Hydrochloride



formation of the α-amino nitriles into the corresponding optically active α-amino acids. The combination of the high efficiency of the Jacobsen-type Strecker reaction with the attractive reaction conditions found for the subsequent hydrolysis makes the whole process interesting for industrial applications. It should be added at this stage that this Jacobsen-type α-amino acid synthesis is commercially applied for the production of optically active α-amino acids at Rhodia ChiRex.

To start with the hydrolysis of the products, obtained by hydrocyanation of aldimines, their transformation into corresponding α-amino acids has been representatively shown for the synthesis of D-*tert*-leucine.[14] Since the direct hydrolysis of the resulting α-amino nitrile is not successful, resulting in a considerable decomposition due to harsh reaction conditions, the amino nitrile has been protected as the *N*-formyl derivative, (*R*)-**24**, in a first step. Subsequently, this compound (*R*)-**24** can be recrystallized to give an enantiomerically pure product, and hydrolyzed using concentrated sulfuric acid without racemization under formation of (*R*)-**25**. The final steps are deformylation, and removal of the *N*-benzyl group using Pd/C yielding the desired enantiomerically pure D-tert-leucine (*R*)-**26** (>99% ee) in a high overall yield of 84% based on imine **17** (Scheme 19).[14]

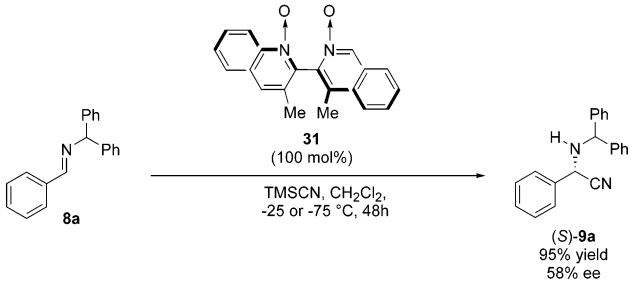
The transformation of the Strecker adducts, obtained by hydrocyanation of ketimines, into optically active quaternary α-amino acids was carried out in a similiar way.[15] Starting from the enantiomerically pure α-amino nitrile (*R*)-**27** (obtained via recrystallization of the corresponding Strecker adduct in 75% yield), subsequent formylation and hydrolysis gave the *N*-benzyl α-methylphenylglycine, (*R*)-**29**. The final step consists of a debenzylation under mild conditions delivering the hydrochloride of D-α-methylphenylglycine, (*R*)-**30**, in 93% overall yield, and with excellent >99.9% ee.[15] The practicability of the method was further shown in the synthesis of enantiomerically pure α-methyl phenylglycine (>99.9% ee) on a gram scale. Thus, this process, based on a Strecker synthesis and subsequent hydrolysis, represents an attractive access to D-α-methylphenylglycine, and to quaternary α-amino acids in general.

2.4.7. Reaction Mechanism

Very recently, the Jacobsen group reported a very detailed structural and mechanistic study.[16] It was found that the Schiff base catalyst **6a** has a well-defined secondary structure in solution. This result has been confirmed by NOE NMR spectroscopic data. The hydrocyanation reaction proceeds according to a Michaelis−Menten kinetic model, with a first-order dependence on **6a** and HCN, and saturation kinetics with respect to the imine substrate. Therefore, a reversible formation of a complex between **6a** and the imine through a hydrogen bond is expected by the authors.[16] As relevant protons involved in this hydrogen bond formations, the two urea hydrogens in **6a** have been identified. In addition, it was found that the Strecker reactions involve binding of the imine as the *Z*-isomer.

Furthermore, a detailed 3D structure of the substrate−catalyst complex supported by molecular modeling revealed that the large group of the imine is directed away from the catalyst. This explains the broad variety of substrates which are tolerated independent of their steric or electronic properties.

Scheme 21. Strecker Reaction Mediated by Chiral *N*-Oxides



A further important hypothesis is that addition of HCN takes place over the diaminocyclohexane framework in **6a**, which led to the prediction that a more bulky amino acid/amide portion should give a further improved catalyst. On the basis of this conclusion, a (model-driven) optimization was carried out revealing the improved catalyst **19** which, as mentioned above, turned out to be the most enantioselective Strecker catalyst prepared to date (for the corresponding preparative results with this catalyst, see Scheme 16 and related text).[16]

2.5. Chiral *N*-Oxides as a "Catalyst"

In principle, also organic molecules without an imine bond appear to be able to catalyze the cyanation of imines. It has been found recently by the Feng group that in the presence of chiral *N*-oxides the reaction of several types of aldimines and trimethylsilyl cyanide furnished the desired α-amino nitriles in yields of up to 95%, and with enantioselectivities in the range of 37−73% ee.[17] However, stoichiometric amounts of the chiral *N*-oxide **31** are required. A representative example using the *N*-oxide **31** is shown in Scheme 21.

In addition to medium enantioselectivities, a drawback of this method is the need for stoichiometric amounts of the chiral *N*-oxide.

2.6. Summary of the Organocatalytic Enantioselective Strecker Reaction

In conclusion, an interesting variety of different types of organocatalysts has been developed which all show a high efficiency in the asymmetric hydrocyanation of imines. These reactions also allow a highly efficient and practical access to optically active α-amino acids. The substrate range is often complementary, thus providing the organic chemist with a tool of catalytic methods to design a broad variety of optically active α-amino nitriles and derivatives thereof, in particular, α-amino acids. An overview about already existing organocatalytic hydrocyanation methods by means of a comparison of the main characteristics is given in the Scheme 22.

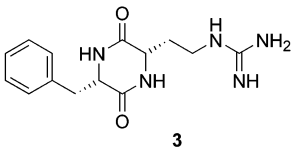
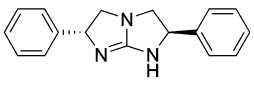
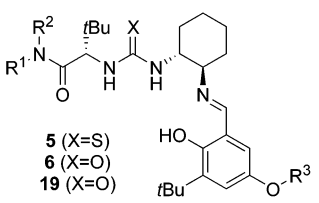
Further advantages of those organocatalysts are the high enantioselectivities and yields that are obtained for the desired products as well as the easy recycling of the organocatalysts.

3. Enantioselective Strecker Reaction Using Metal Catalysts

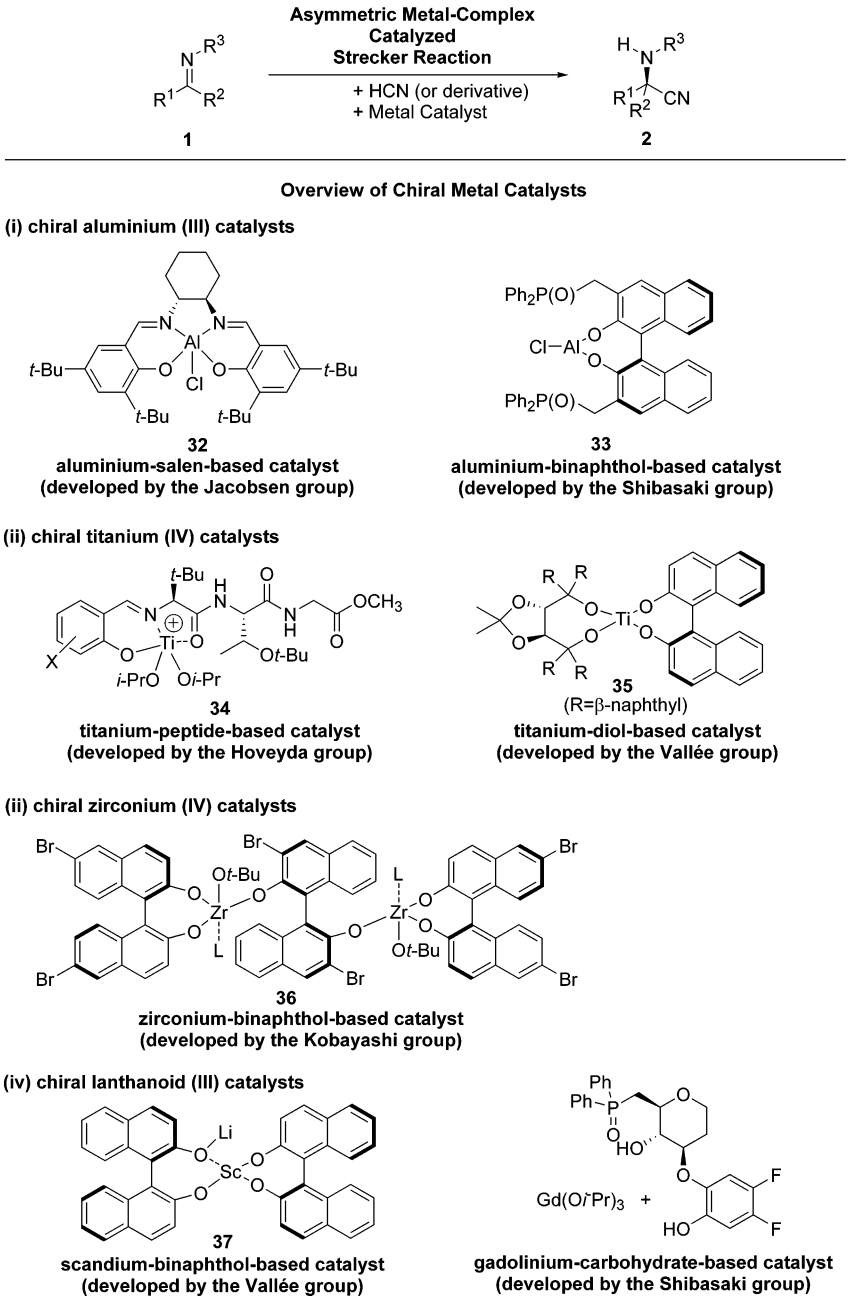
3.1. Overview

The ability of chiral metal complexes to act as versatile catalysts for a broad variety of synthetic transformations is widely known.[5,28] Representative examples are the asymmetric Corey-Bakshi-Shibata reduction (CBS reduction),[29] the Mukaiyama aldol reaction,[30,31] the Sharpless epoxidation[32] and dihydroxylation,[33] the Jacobsen epoxidation,[34] the Noyori hydrogenation,[35] as well as the asymmetric C−C bond forming reactions using the Sibasaki heterobimetallic catalysts.[36] Some of those methods already proved their technical feasibility. However, it took until 1998 when the first asymmetric metal complex-catalyzed Strecker reaction was reported.[37] In recent years, several groups contributed to the development

Scheme 22. Summary of the Organocatalytic Strecker Reaction

catalyst structure	substrate range	catalytic amount	range of yield [%]	range of ee [%]
 **3**	aromatic aldimines (not NO_2- subst. and heteroatoms)	2 mol%	82-97	80-99
 **4**	aromatic, aliphatic aldimines	10 mol%	80-99	50-88
 **5** (X=S) **6** (X=O) **19** (X=O)	aromatic, aliphatic aldimines and ketimines	1-2 mol%	65-98 45-100	77-99 42-95

Scheme 23. Overview of Chiral Metal Catalysts



of succcessful chiral metal catalysts for the asymmetric catalytic Strecker reaction. An overview of the types of applied Lewis acid catalysts, which comprises aluminum, titanium, zirconium, and lanthanoid complexes, is given in Scheme 23.

It is noteworthy that each catalyst requires the use of a specific *N*-substituent for obtaining good results. Thus, the preferred type of *N*-substituent depends on the type of applied catalyst.

3.2. Chiral Aluminum(III) Complexes as a Catalyst

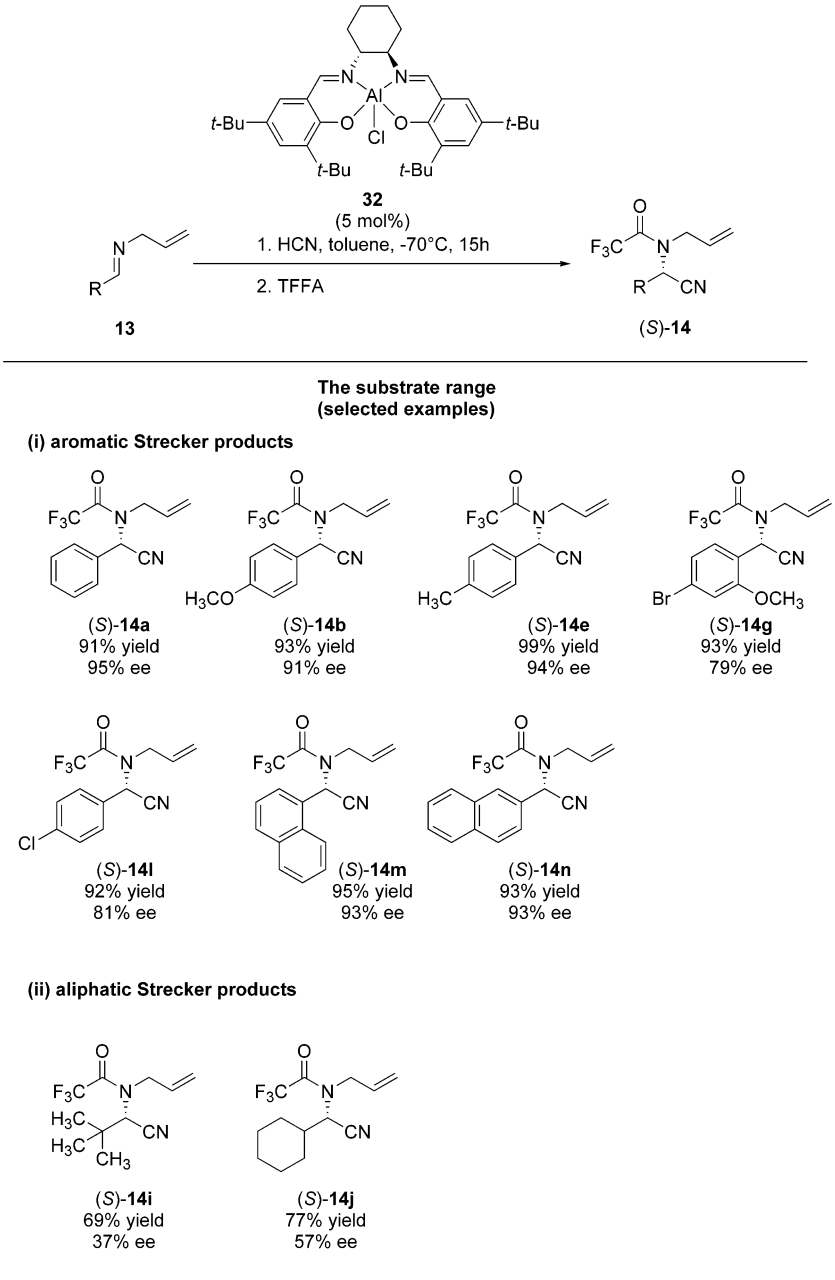
3.2.1. Aluminum(III)-Salen-Based Catalysts

The Catalytic Concept. The suitability of chiral salen complexes to act as efficient catalysts for asymmetric epoxidation[34] and kinetic resolution[38,39] has been impressively demonstrated by the Jacobsen group. Both of those processses found industrial applications at Rhodia ChiRex underlining the high degree of efficiency of those salen-based catalysts. In addition, metal−salen complexes turned out to be suitable catalysts also for numerous other reactions, including the hydrocyanation of aldehydes. Recently, the Jacobsen group successfully extended the application range of those exceptional catalysts toward the first metal-catalyzed asymmetric Strecker reaction.[37]

A first screening using TMSCN as donor and *N*-allyl benzaldimine as a substrate revealed that in the presence of a salen ligand, aluminum is the most promising metal component. Since under strictly anhydrous conditions, no reaction was observed, it appeared that HCN is the reacting species rather than TMSCN.

When carrying out the reaction at −70 °C in toluene, the corresponding trifluoroacetamide deriva-

Scheme 24. Strecker Reaction Using the Jacobsen-Type Aluminum Catalyst



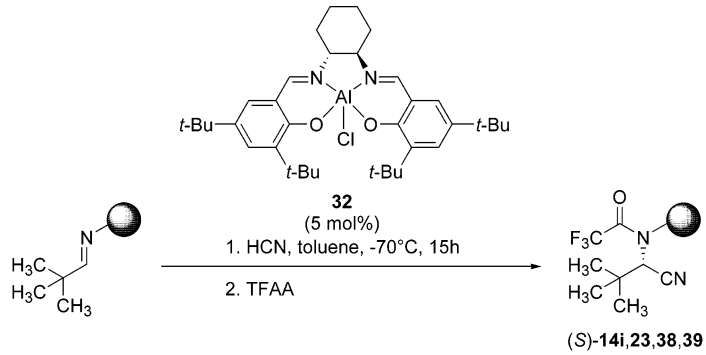
tive of the α-amino nitrile, (*S*)-**14a**, was obtained in 91% yield and with 95% ee (Scheme 24).[37,40] The derivatization turned out to be necessary due to instability of the α-amino nitriles during workup (which undergo racemization upon exposure to silica gel). On the basis of this efficient reaction system, a broad range of *N*-allyl imines **13** was investigated using a catalytic amount of 5 mol %.

The Substrate Range. In general, good yields accompanied by enantioselectivities in a moderate to excellent range were obtained (Scheme 24).[37,40] Benzaldimine, **13a**, and *p*-substituted derivatives thereof represented very good substrates with excellent yields in the range of 91−99% and enantioselectivities of 79−95% ee. For example, the *p*-methyl-substituted aromatic amino nitrile (*S*)-**14e** is formed with 94% ee, and naphthyl-based amino nitriles, (*S*)-**14m** and (*S*)-**14n**, are obtained in high yields in the range of 93−95%, and with 93% ee. In contrast, the asymmetric hydrocyanation of alkyl imines resulted in the formation of the corresponding amino nitrile products with considerably lower yields and enantioselectivities. For example, the amino nitrile (*S*)-**14i**, which represents an interesting precursor for the pharmaceutically important α-amino acid L-*tert*-leucine,[21] was obtained in 69% yield, but with only 37% ee.[37]

To improve the results for alkyl imines, the influence of the type of *N*-substituent has been investigated. Interestingly, the *N*-substituent did not show a significant influence on the enantioselectivity (Scheme 25). The best result was obtained with a *N*-benzyl substituted imine which led to the desired α-amino nitrile (*S*)-**23** in 88% yield and with 49% ee.[37] The enantioselectivity could be dramatically improved by a simple recrystallization obtaining the product in 48% yield, and with a high enantiomeric excess of 97.5% ee.

Transformation into α-Amino Acids. The synthetic utility of this aluminum−salen complex-

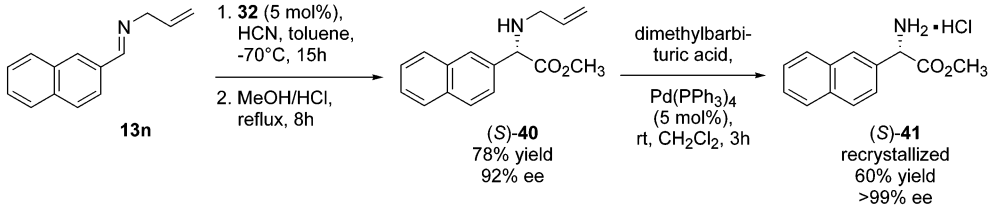
Scheme 25. Influence of Protecting Groups in the Presence of the Jacobsen-Type Aluminum Catalyst



entry	= protecting group	product	yield [%]	ee [%]
1	allyl	(*S*)-**14i**	69	37
2	benzyl	(*S*)-**23**	88 (48)[a]	49 (97.5)[a]
3	*p*-methoxybenzyl	(*S*)-**38**	67	44
4	*o*-methoxybenzyl	(*S*)-**39**	74	40

a) The yield, and ee value shown in parantheses refer to the recrystallized product.

Scheme 26. Deallylation and Synthesis of an Amino Acid Ester Hydrochloride

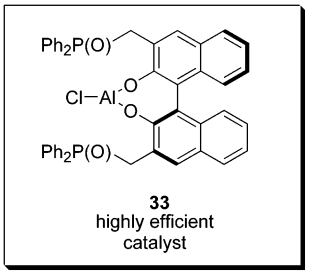


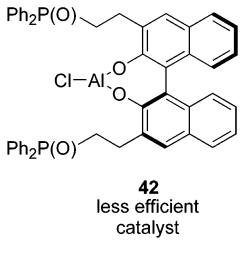
catalyzed Strecker reaction for the preparation of optically active α-amino acids has been also demonstrated by the Jacobsen group. Starting from the imine **13n**, an asymmetric hydrocyanation gave the optically active α-amino nitrile, (*S*)-**14n**, which was subsequently hydrolyzed into the α-amino acid ester (*S*)-**40** in 78% yield (for both steps) and with 92% ee (Scheme 26).[37] It is noteworthy that a low catalytic amount of only 2 mol % was used, and that a chromatographical work up is not required. In addition, this reaction was carried out on a 6 mmol scale. A subsequent one-step conversion of the ester (*S*)-**40** by Pd(0)-catalyzed deallylation gave the desired α-amino acid ester hydrochloride (*S*)-**41** in 60% yield, and with >99% (after recrystallization).

3.2.2. Aluminum(III)-Binaphthol-Based Catalysts

The Catalytic Concept. For several asymmetric catalytic reactions, it has been found that rational designed bifunctional complexes represent promising catalysts due to the attachment of both electrophilic and nucleophilic substrates to the chiral catalyst in the transition state complex.[41] Such a coordination of both substrates within an asymmetric space can lead to a stronger stereodiscrimination, resulting in a highly enantioselective process. Several "bifunctional" concepts have been developed in the past for catalytic asymmetric reactions.[42] Recently, this concept of bifunctional catalysts has been extended by Shibasaki et al. to another interesting class of chiral catalysts which were successfully applied in asymmetric cyanation reactions, namely, the concept of monometallic, phosphinoyl-containing catalysts of type **33** with Lewis acid and Lewis base properties (Scheme 27).[43,44]

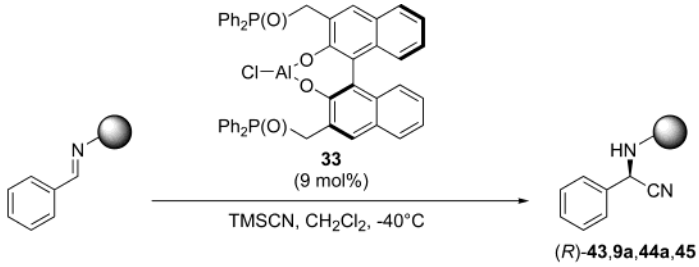
Scheme 27. Overview of Bifunctional Aluminum Catalysts





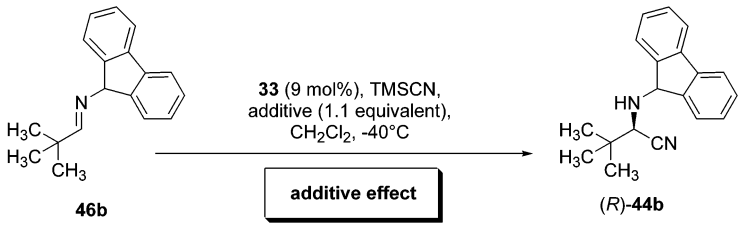
This type of Lewis acid−Lewis base catalyst **33** has been originally developed for the cyanohydrin synthesis,[43−46] and gave the products in high yields and with excellent enantioselectivities. Interestingly, the related homologue catalyst **42** (Scheme 27), bearing a $(CH_2)_2P(O)Ph_2$ group instead of a $CH_2P(O)Ph_2$ functionality, did not give satisfactory results, underlining the need for a fine-tuned catalyst. The structural key characteristics for an efficient catalyst have been well understood, and a subsequent rational optimization of the catalyst was sucessfully carried out. In the presence of the optimized catalyst, **33**, the

Scheme 28. Influence of *N*-Protecting Groups in the Presence of the Shibasaki-Type Aluminum Catalyst



entry	= protecting group	product	yield [%]	ee [%]
1	allyl	(*R*)-**43**	67	4
2	benzhydryl	(*R*)-**9a**	84	78
3	fluorenyl	(*R*)-**44a**	97	95
4	triphenylmethyl	(*R*)-**45**	traces	---

Scheme 29. The Effect of Additives



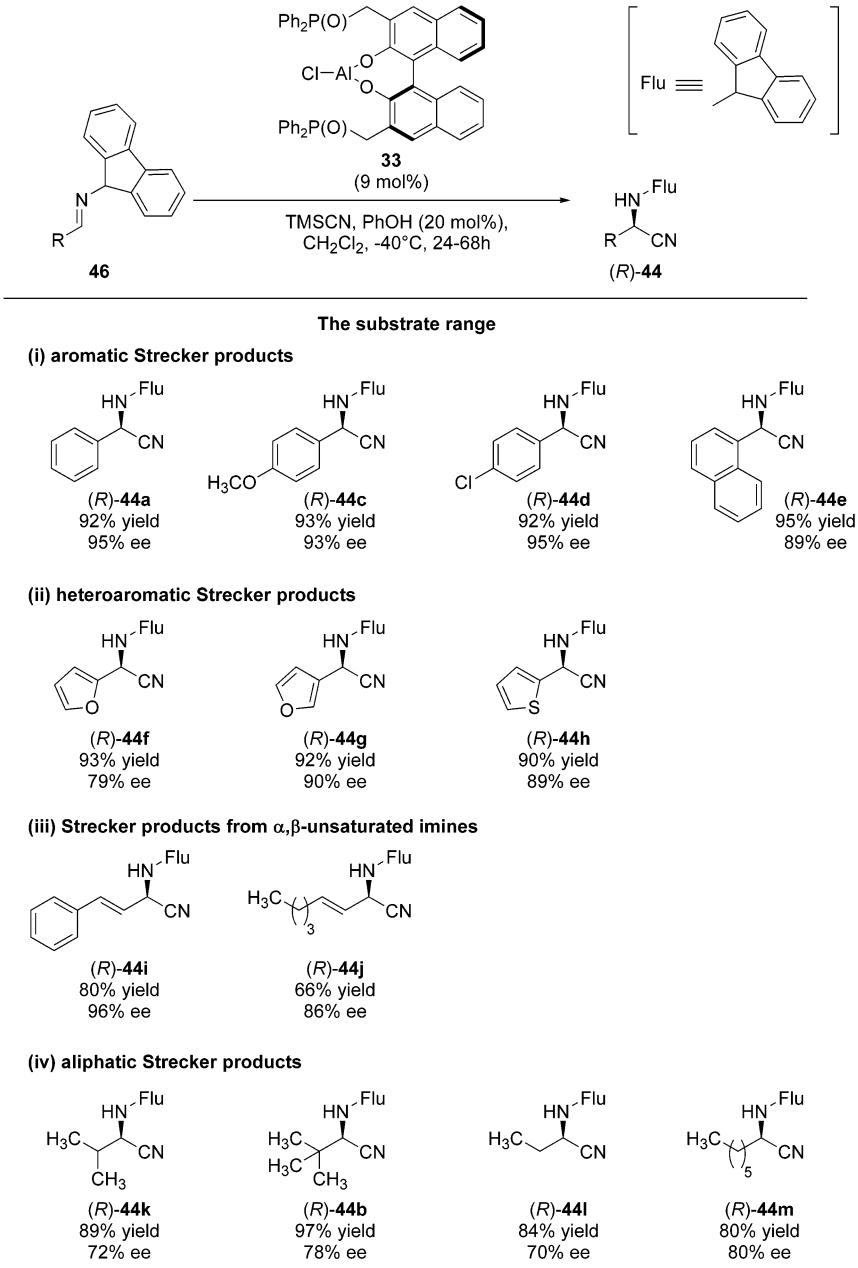
entry	additive	yield [%]	ee [%]
1	-----	94	75
2	MeOH	94	66
3	*i*-PrOH	96	68
4	*tert*-BuOH	97	72
5	PhOH	99	78
6	(*R*)-1-phenylethanol	90	64
7	(*S*)-1-phenylethanol	91	67

asymmetric hydrocyanation of aldehydes proceeds under formation of the products in high yields and with up to 98% ee.[43]

The extension of this asymmetric cyanosilylation of carbonyl compounds toward the corresponding reaction with imines represented the next step.[47] A particular focus of the Shibasaski group was on the Strecker reaction using α,β-unsaturated imines, which have not been used before, and aliphatic *N*-aldimines, which gave nonsatisfactory enantioselectivities when applying previous methods. The first initial attempts in applying the catalyst for the Strecker reaction using TMSCN as a cyanide donor revealed a significant effect of the nitrogen substituent.[48] In the model reaction of several types of *N*-substituted benzaldimines, a negligible enantioselectivity of only 4% ee was found when using a benzaldimine bearing an *N*-allyl substituent (which, in contrast, led to high enantioselectivities in the case of the Jacobsen Al(III) catalyst). The breakthrough in the asymmetric cyanation with the Shibasaki catalyst, **33**, was achieved when using the analogue *N*-benzhydryl benzaldimine and *N*-fluorenyl benzaldimine, respectively (Scheme 28; entries 2 and 3).[48] For the resulting products, (*R*)-**9a** and (*R*)-**44a**, high enantioselectivities of 78 and 95% ee, respectively, were obtained. In the latter case, the yield was also in an excellent range of 97%. Interestingly, the more bulky *N*-triphenylmethyl benzaldimine did not afford the desired product, (*R*)-**45**, even at room temperature. This indicates that the *N*-fluorenyl group is the preferred *N*-substituent. The dependency of the ee value from the type of *N*-substituent is summarized in Scheme 28.[48]

Subsequently, the reaction has been further optimized, and an important additive effect was found. In the presence of (achiral) protic additives such as alcohols and phenol, a beneficial effect on the reaction rate was observed (Scheme 29).[47,48] Slow addition of the additive is a prerequisite for good results. When adding phenol over a period of 22 h, the best result was obtained with 99% yield and with 78% ee.

Scheme 30. The Substrate Range of the Shibasaki-Type Aluminum Catalysts



Aliphatic alcohols as an additive also gave high yields of at least 94%, but enantioselectivities were somewhat lower in the range of 66−72%.

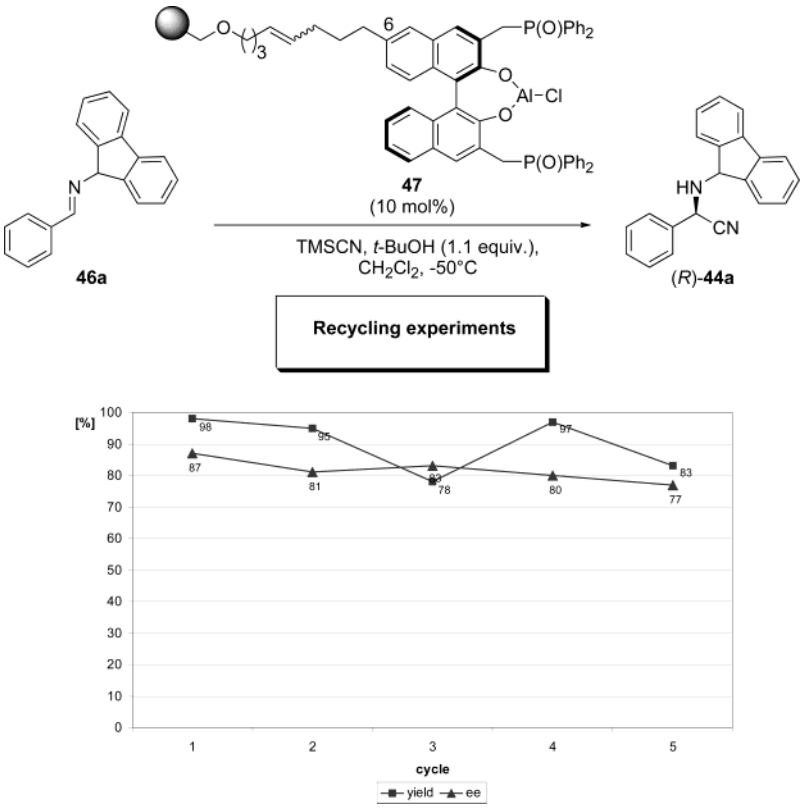
Both enantiomers of a chiral alcohol, namely, 1-phenylethanol, were tested, but did not give any improvement. Since comparable results in the range of 64−67% ee were found, the enantiospecificity of the chiral additive does not appear to play a significant role. It is noteworthy that the amount of the additive PheOH could be decreased from 110 to 20 mol %. An overview of the additive effect is given in Scheme 29.[47,48]

The Substrate Range. The Shibasaki group applied this asymmetric catalytic Strecker reaction toward the synthesis of a broad variety of α-amino nitriles, (*R*)-**44**.[47,48] It was found that a broad range of imine substrates are tolerated. An overview of synthetic examples is shown in Scheme 30. Benzaldehyde-derived imine, **46a**, and *p*-substituted derivatives thereof are excellent substrates and gave the Strecker products (*R*)-**44a**,**c**,**d** in yields of 92−93%, and with high enantioselectivities of 93−95% ee. In addition, naphthyl and heteroaromatic imines have been successfully converted into the corresponding products (*R*)-**44e**−**h** in high yields, and with enantioselectivities in the range of 79−90% ee.

Furthermore, this catalytic reaction proceeds well with aliphatic *N*-aldimines and α,*β*-unsaturated imines. Several aliphatic α-amino nitriles of type (*R*)-**44b**,**k**−**m** could be obtained in optically active form with enantioselectivities of 70−80% ee.[47,48] In addition, the yields were excellent in the range of 80−97%.

Applying the bifunctional catalyst **33** in the asymmetric Strecker-type reaction with α,*β*-unsaturated imines enables the preparation of the corresponding α-amino nitriles (*R*)-**44i**−**j** in good yields of up to 80% and with ee values in the excellent range of 86−96%.

Scheme 31. Recycling Studies



As mentioned above, these types of products are difficult to synthesize by other methods. In addition, this contribution by the Shibasaki group represents the first example of a catalytic asymmetric hydrocyanation of α,β-unsaturated imines.

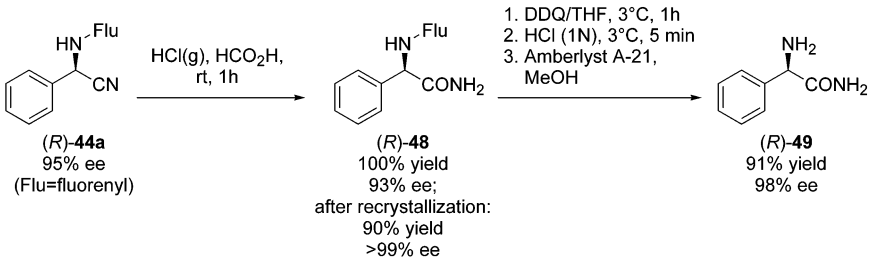
Process Development Studies: Switch of the Cyanide Source and Immobilization of the Catalyst. It is noteworthy that TMSCN as well as HCN (in the presence of 20 mol % TMSCN) can act as a cyanide donor, albeit TMSCN appears to be the reactive nucleophile (see also mechanistic section below). This has been underlined by a significant difference of reactivity in case of TMSCN and HCN (which reacts much more slowly). However, also the use of HCN as a nucleophile is possible when adding a small amount of TMSCN (20 mol %). In this case, phenol is not needed as an additive. Under those conditions, the Strecker reaction proceeds in a similiar manner, leading to the α-amino nitrile products, (*R*)-**44**, in comparable yields and enantioselectivities.[47,48]

An interesting extension of this concept toward an asymmetric Strecker reaction with an immobilized Lewis acid/Lewis base catalyst of type **47** (Scheme 31) was also reported by Shibasaki and co-workers.[49] Immobilized types of efficient asymmetric catalysts are in general highly desirable with respect to separation of the catalysts from the reaction mixture, and reusability of the catalyst. In the presence of the polymer-supported catalyst **47** possessing a sufficiently long spacer at the 6-position, the asymmetric hydrocyanation of imines proceeds well with enantioselectivities of 83−87%. Although the enantioselectivities are slightly lower compared with those of the soluble "homogeneous analogue" **33**, the reactivity of the solid-supported bifunctional catalyst **47** is in a similiar range. In addition, recycling studies were carried out showing that the catalyst could be recycled at least four times.[49] However, the enantioselectivity decreased from 87 to 77% after five cycles, and the macroscopic structure was broken after several recyling cycles. In addition, longer reaction times were required after three reaction cycles.

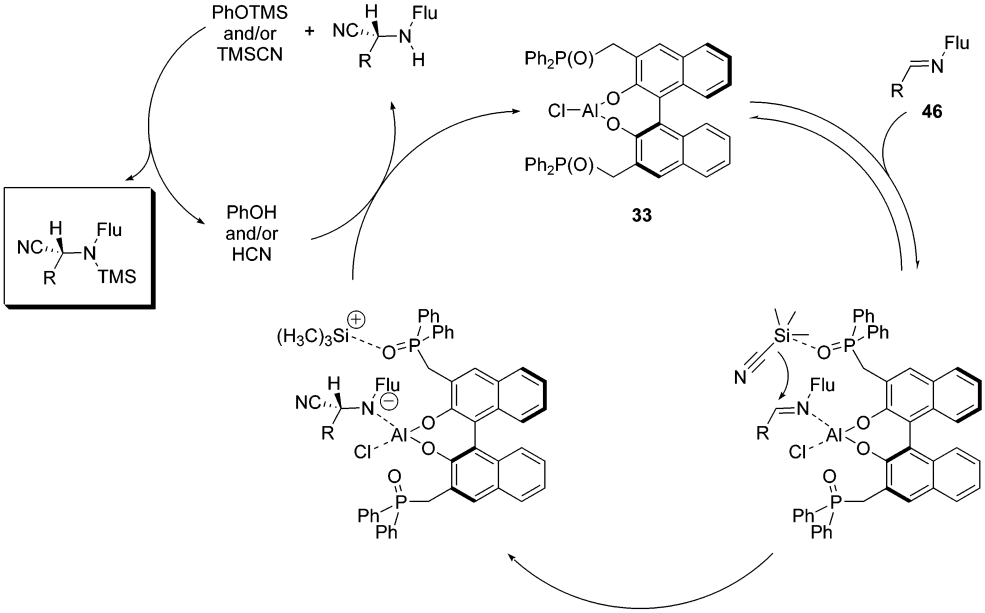
Transformation of the Amino Nitriles into α-Amino Acid Amides. The products (*R*)-**44** can be successfully converted into the pure amino acid amides of type (*R*)-**49** by subsequent cleavage of the protecting group. A representative example is shown in Scheme 32. The desired phenylglycine amide, (*R*)-**49**, was obtained after hydrolysis and cleavage of the *N*-substituent in a high yield of 91%, and with an excellent enantioselectivity of 98% ee.[47]

The Reaction Mechanism. The Shibasaki group also carried out a detailed study of the reaction mechanism.[47,48] To get insight into the role of the additive PhOH, the kinetic profile of the reaction was investigated. It has been found that in the presence of 20 mol % of PhOH the initial reaction rate is 82 times faster than in the absence of PhOH. However, after a conversion of 20%, the reaction rate remarkably decreased, which has been explained by complete consumption of the 20 mol % of PhOH under formation of TMSOPh. These results indicate that PhOH acts as a proton source. In addition, a comparison of the reaction rates clearly showed that TMSCN is the reactive nucleophilic cyanide donor rather than HCN. The latter compound, HCN, may be generated in situ by the reaction of TMSCN with PhOH. Thus, the role of PhOH and/or HCN is to act as a proton source for protonation of the negative

Scheme 32. Synthesis of (*R*)-Phenylglycine Amide



Scheme 33. Reaction Mechanism



charge on the nitrogen atom which is generated in the cyanide addition step. The corresponding proposed reaction mechanism is shown in Scheme 33.

Since it has been also found that HCN can act as such a proton source (instead of PhOH), Shibasaki and co-workers made use of this effect by applying a mixture of HCN (120 mol %)/TMSCN (20 mol %) as a cyanide source.[47,48] As described above, comparable results have been obtained with this economically more attractive system.

It should be added that the higher reactivity of TMSCN compared to HCN is caused by the unique feature of this bifunctional catalyst. The trimethylsilylcyanide interacts with the phosphane oxide moiety of the Lewis base catalyst. The corresponding activated TMSCN then represents an efficient cyanide donor.

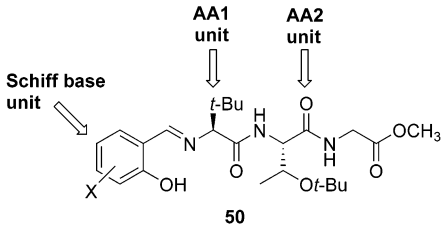
In addition, the aluminum metal center is assumed to work as a Lewis acid, thus activating the imine component. Thus, in the transition state both substrates are coordinated to the monometallic, bifunctional catalytic complex. The subsequent transfer of the cyanide to the aldehyde takes part in a highly enantioselective manner. This dual Lewis acid−Lewis base activation pathway has also been supported by kinetic studies.[47,48]

3.3. Chiral Titanium(IV) Complexes as a Catalyst

3.3.1. Titanium(IV)-Peptide-Based Catalysts

The Catalytic Concept. The Hoveyda group focused on the development of a catalytic asymmetric Strecker synthesis of α-amino nitriles which can be easily converted subsequently in one step into the desired enantiomerically pure α-amino acids.[50,51] In this one-step conversion, the hydrolysis of the cyano group as well as the cleavage of the *N*-substituent is carried out. As target intermediates, *N*-benzhydryl-substituted α-amino nitriles, **9**, were chosen. In a preliminary screening with the modular chiral tripeptide ligand of type **50** (Scheme 34), and numerous

Scheme 34. Modular Chiral Tripeptide Ligands for the Hoveyda-Type Titanium Catalyst

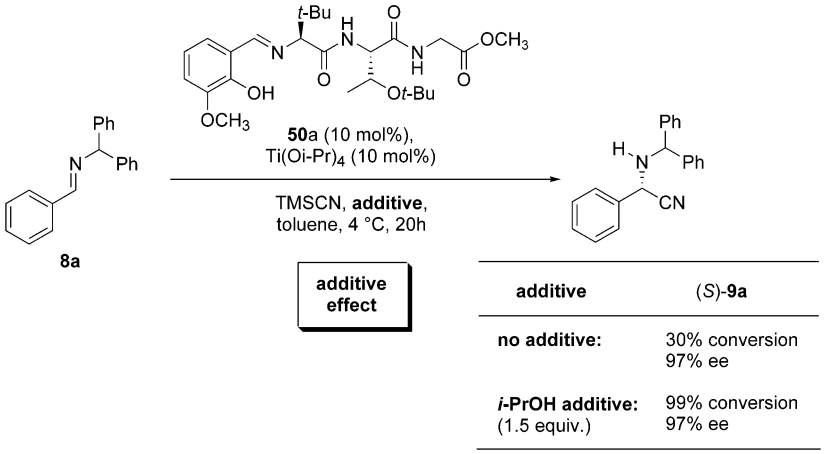


50

(**50a**: X=5-OMe; **50b**: X=3,5-DiCl; **50c**: X=3,5-DiBr; **50c**: X=1-naphthyl)

metal alkoxides (using, however, *N*-benzylimines as an imine component) it turned out that titanium was the most promising metal component. During optimization of the reaction conditions, toluene was found as a preferred less volatile and environmental acceptable solvent, and TMSCN was the preferred cyanide donor. It is noteworthy that the Strecker reaction was carried out at 4 °C. Thus, very low temperatures of, e.g., −40 or −70 °C, are not re-

Scheme 35. The Effect of *i*-PrOH as an Additive



quired, which is advantageous with respect to a potential large scale application.[50]

Applying a previously developed ligand optimization protocol,[52−54] for each substrate the most suitable tripeptide ligand of type **50a**−**c** was found (Scheme 34). This ligand screening showed that a *tert*-leucine group in the AA1 site as well as a threonine derivative in the AA2 position are the optimized moieties for those positions.[50] However, different substituents were found to give the best results for the Schiff base moiety dependent on the type of substrate.

Under those reaction conditions and in the presence of 10 mol % of the titanium isopropoxide and ligand, respectively, the α-aminonitriles of type **9** were formed dependent on the substitution pattern with promising enantioselectivities of 84−97% ee.[50] However, the reaction time was long (2 days), and the resulting conversions were only in the range of 15−39%. For example, the Strecker product (S)-**9a** was obtained with a low conversion of only 30%, albeit enantioselectivity (97% ee) was high (Scheme 35).

The breakthrough with respect to high yields was achieved after discovering a beneficial additive effect.[50] In recent years, in many asymmetric catalytic reactions the reactivity was improved after addition of a nonchiral additive (which is often a simple molecule).[55] The Hoveyda group focused on a screening of protic additives due to an expected potentially faster cleavage of the Ti−N bond, and removal of the TMS group within the Ti complex during the catalytic cycle.[50] Thus, a more facilitated regeneration of the catalyst was expected by means of a protic additive. After investigating several protic additives, it was found that the reaction rate was greatly enhanced when carrying out the Strecker reaction in the presence of 1.5 equiv of *i*-PrOH. It turned out that the benefical effect of *i*-PrOH is based on its ability to cleave TMSCN under in situ formation of HCN, which is the reactive cyanide nucleophile (for details, see the section about the reaction mechanism below). For example, the aromatic Strecker product (*S*)-**9a** was formed with a conversion of 99% and with 97% ee. The influence of the additive is exemplified in Scheme 35 for the synthesis of (*S*)-**9a**.[50]

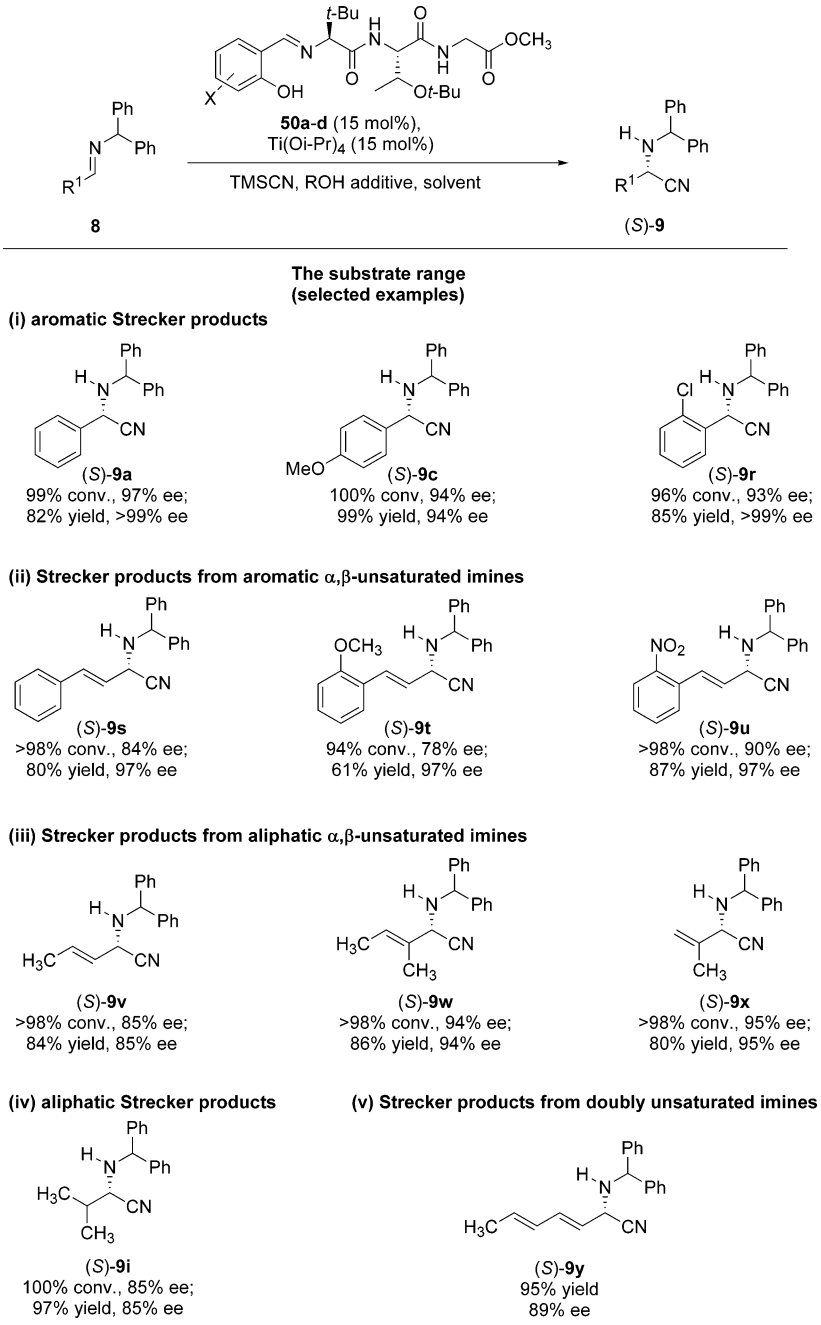
The Substrate Range. The products were formed with remarkably increased, excellent conversions in a range between 93 and 100%, and with still high enantioselectivities of 84−97% ee.[50] In some cases, ee values were improved as well. Albeit most of the substrates are aryl-imines, the Hoveyda group showed that alkyl imines can also be used (Scheme 36). This has been representatively shown for the synthesis of (*S*)-**9i** (97% yield, 85% ee), which is an intermediate for the synthesis of the nonproteinogenic α-amino acid L-*tert*-leucine.[50]

A reduction of the catalytic amount from 10 to 5 mol % led to comparable results (for product (*S*)-**9c**: 5 mol %: 98% conversion, 94% ee, 22 h), whereas a slightly decreased enantioselectivity of 84% and a longer reaction time (99% conversion after 42 h) was observed when lowering the catalytic amount further to 2.5 mol %.

Enantiomerically pure samples can be easily obtained after work up when a simple recrystallization step is included in the downstream process. After recrystallization, the purified products, e.g., (*S*)-**9a**,**c**,**r**, were not only obtained with excellent enantioselectivities of >99% ee, but also in high yields of >80%.[50] A graphical overview of the enantiomerical enrichment is given in Scheme 36. In some cases, however, column chromatographical work up was used in the downstream process.

An extension of this efficient Strecker reaction technology toward the addition of a cyanide donor to aromatic and aliphatic α,β-unsaturated imines was also reported by the same group.[51] The resulting products (*S*)-**9s**−**x**, which represent precursors for biologically active β,γ-unsaturated α-amino acids, are difficult to prepare by other methods, in particular, by asymmetric hydrogenation. The selective addition of TMSCN to the C=N double bond requires a highly regioselective and enantioselective catalyst. Screening titanium-tripeptide catalysts (10 mol %), prepared from $Ti(OiPr)_4$, and tripeptides of type **50**, revealed that the tripeptide **50d** based on the bulky naphthyl-substituted Schiff base is the most promising ligand when using the α,β-unsaturated imine **8s** as a substrate.[51] The resulting amino nitrile (*S*)-**9s** was formed with >98% conversion, and with an enantioselectivity of 84% ee. After recrystallization, the product (*S*)-**9s** was isolated in 80% yield, and with 97% ee. The regioselectivity is very high since the amount of the regioisomer (1,4-adduct) is below 2%.

Scheme 36. The Substrate Range of the Hoveyda-Type Titanium Catalyst



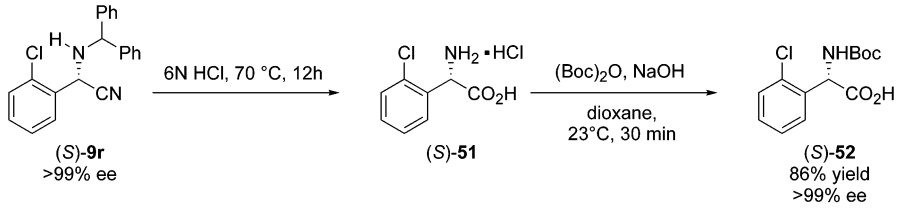
Starting from other aromatic substrates, the analogue Strecker reaction gave the desired products (*S*)-**9t**−**u** with conversions of at least 94%, and with enantioselectivities in the range of 78−90% ee.[51] In most cases, enantiomeric excess could be increased up to 97% by recrystallization. Several examples are shown in Scheme 36. In general, the electron-rich α,*β*-unsaturated imines gave lower enantioselectivities. In those cases, reactions were performed at lower reaction temperatures to increase the enantioselectivity.

When carrying out the reactions with several aliphatic α,*β*-unsaturated imines, **8v**−**x**, excellent conversions (>98%) as well as high enantioselectivities in the range of 85−95% ee were achieved for the products (*S*)-**9v**−**x** (Scheme 36), albeit a higher catalytic amount of 15 mol % was required.[51] In these cases, however, a recrystallization did not lead to an improvement of the enantiomeric excess. The highest level of enantioselectivity for aliphatic α,*β*-unsaturated imines was obtained when imines bearing a substituent at the α-positions are used.

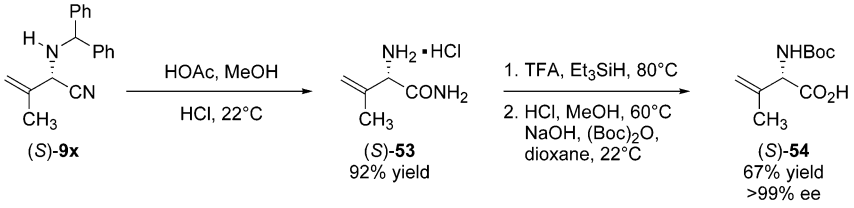
Furthermore, the Hoveyda-type Strecker reaction was applied for the hydrocyanation of doubly unsaturated imines. In the presence of 15 mol % of Ti(O*i*-Pr)$_4$ and ligand **50a**, the desired product (*S*)-**9y** was obtained in 95% yield and with an enantioselectivity of 89% ee.[51]

Transformation into α-Amino Acids. As mentioned above, a particular advantage of those optically active *N*-benzhydryl amino nitriles of type **9** is the possibility to perform the transformations of CN

Scheme 37. Synthesis of an *N*-Boc-Protected Amino Acid



Scheme 38. Transformation of an Unsaturated Amino Nitrile into Its *N*-Boc-Protected Amino Acid



hydrolysis and amine deprotection in a single operation (see also section 2.2). This has been successfully demonstrated by the Hoveyda group for the synthesis of the *N*-Boc-protected α-amino acid L-(*o*-chloro)-phenylglycine, (*S*)-**52** (Scheme 37).[50] Starting from (*S*)-**9r**, the *N*-Boc-protected α-amino acid (*S*)-**52** was formed in a two-step procedure in 86% yield, and with >99% ee. The first step consists of the transformation of (*S*)-**9r** into the α-amino acid hydrochloride (*S*)-**51**, followed by *N*-protection. A loss of enantiomerical purity during derivatization was not observed.

The conversion of the unsaturated amino nitriles (*S*)-**9s**−**x** into its corresponding amino acids, however, turned out to be more difficult compared with the aromatic and aliphatic products mentioned above.[51] A representative example is given in Scheme 38. Thus, smoother reactions conditions were chosen for the CN hydrolysis resulting in the formation of the amide as an intermediate.

Very recently, a further interesting application of the titanium(IV)-complex catalyzed Strecker reaction has been developed by the Hoveyda group.[56a] The resulting optically Strecker product was used as an intermediate for the synthesis of chloropeptin-1, which is a potent anti-AIDS agent. Notably, this synthetic route, comprising the Hoveyda-type Strecker reaction as a key step, represents the first total synthesis of this target molecule, chloropeptin-1.

Studies on the Reaction Mechanism. A detailed investigation of the reaction mechanism has been carried out by the Hoveyda group comprising kinetic, structural, and stereochemical data.[56b] A very important result of this study is the fact that the Hoveyda catalysts appear to be indeed bifunctional catalysts. The imine is coordinated by the titanium (attached to the Schiff base in the ligand), and the amide functionality (within the peptide ligand) associates and delivers HNC to the activated imine component. The mechanistic studies revealed that the hydrogen bonding likely involves the N−H bond of HNC, and not the C−H bond of HCN. This type of substrate−catalyst ensemble is shown graphically in Figure 1. In addition, further kinetic data underlined that this asymmetric catalytic Strecker reaction proceeds via a highly organized transition structure as the rate-limiting step.

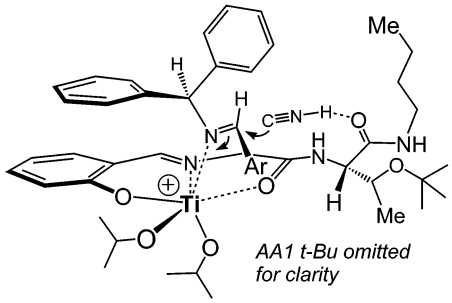


Figure 1. Substrate-catalyst ensemble; reprinted with permission from ref 56. Copyright American Chemical Society.

A key feature of this titanium-catalyzed Strecker reaction is the slow addition of an additive, indicating that the really reactive cyanide nucleophile is HCN rather than TMSCN. This hypothesis has been underlined by similiar results which were obtained when adding HCN slowly to the reaction mixture.[50,56b] Slow addition of HCN (or *i*-PrOH when using TMSCN) guarantees a low permanent concentration of HCN, and, thus, a minimal level of noncatalyzed (nonasymmetric) reaction which would furnish the racemate.

Furthermore, the Hoveyda group focused on the clarification of whether the catalytically active species is monomeric or dimeric (or oligomeric). Since a kinetic study revealed that the Strecker reaction is first order, a monomeric catalyst structure is likely involved in the reaction pathway.[56b]

The structural features of the chiral peptide ligand within the titanium catalyst (see structure **55** in Figure 1 above) play a key role with respect to enantioselectivity and reactivity. The presence of the AA2 moiety is a prerequisite for high yields and enantioselectivities as has been shown in comparison experiments using analogous ligands without such a AA2 moiety.[56b] The presence of a more Lewis basic amide (compared with a carboxylic acid ester) enhances the rate of cyanide addition.

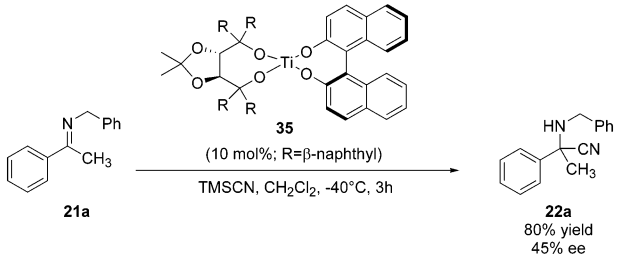
3.3.2. Titanium(IV)-Diol-Based Catalysts

A different type of titanium catalyst has been investigated for its potential to catalyze the asymmetric Strecker reaction using ketimines as a sub-

strate.[57] As a suitable catalyst for the addition of TMSCN to *N*-benzyl methylphenylimine, **21a**, as a model substrate, the Valleé group screened among different types of titanium(IV)-TADDOL-based complexes.

The highest yield (95%) and an enantiomeric excess of 31% was obtained when using a titanium complex based on mixture of (phenyl-substituted) TADDOL, and (*S*)-binaphthol as ligands. Interesting, replacing (*S*)-binaphthol by the opposite (*R*)-enantiomer gave the same yield, but ee was lower (13% ee). The highest enantioselectivity (45% ee) under those reaction conditions and a yield of 80% were achieved with a titanium complex, **35**, containing β-naphthyl substituted TADDOL, and (*R*)-binaphthol as ligands (Scheme 39). Notably, the reaction time was very short, only 3 h.[57]

Scheme 39. The Vallée-Type Strecker Reaction with Titanium Catalysts



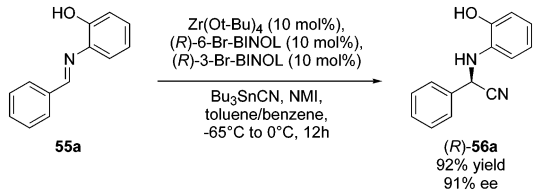
Other types of titanium-diol catalysts, which are based on BINOL and BIPOL as ligands, were also applied. However, in general a moderate conversion of 50% and a very low enantioselectivity of 12% ee was found. Further attempts to improve the enantioselectivity by addition of suitable additives resulted in the formation of the corresponding product with 80% yield, and with 59% ee when using TMEDA as an additive. Albeit enantioselectivity still has to be improved, the short reaction times of only 1−3 h are interesting.[57]

3.4. Chiral Zirconium(IV) Complexes as a Catalyst

3.4.1. The Catalytic Concept

A concept for the asymmetric Strecker reaction which is based on the use of chiral zirconium (IV) catalysts has been developed by the Kobayashi group.[58] The same group reported previously the application of Zr(IV)-BINOL-based complexes in the catalytic asymmetric Mannich reaction,[59,60] and Diels−Alder reaction,[61] respectively. At first, a screening of different types of catalysts, prepared from Zr(O*t*-Bu)$_4$, *N*-methylimidazole (NMI), and 2 equiv of a 3,3′- or 6,6′-disubstituted binaphthol (or mixtures of different binaphthol derivatives thereof) has been carried out for the conversion of aldimine **55a** with tributyltin cyanide.[58] Surprisingly, a 1:1 mixture of two binaphthols, namely (*R*)-3,3′-dibromo-1,1′-binaphthol, and (*R*)-6,6′-dibrom-1,1′-binaphthol, gave the best results. The desired α-amino nitrile derivative (*R*)-**56a** was obtained in 92% yield, and with an enantioselectivity of 91% ee. As a substrate, the imine derived from the reaction of benzaldehyde and *o*-anisidine was used. This optimized model reaction is shown in Scheme 40.[58]

Scheme 40. Kobayashi-Type Strecker Reaction



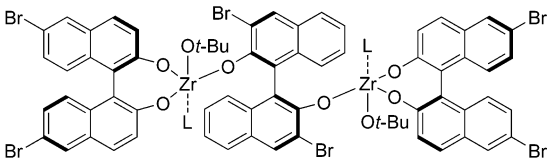
The resulting *o*-methoxyphenyl group as an *N*-substituent was found to be beneficial for high asymmetric induction in previous reactions with the Kobayashi Zr-catalysts.[7] Those types of imines bearing a methoxy group are able to coordinate to the zirconium through the methoxy and the imino group. The resulting chiral zirconium−imine complex is then able to produce higher enantioselectivities due to a more rigid conformation.[58] Accordingly, not only a high enantioselectivity but also a high yield was obtained for the resulting product (*R*)-**56a**.

It is noteworthy that the structure of the catalytical active species which results from the above-mentioned mixture (1 equiv each of Zr(O*t*-Bu)$_4$, *N*-methylimidazole (NMI), (*R*)-3,3′-dibromo-1,1′-binaphthol, and (*R*)-6,6′-dibrom-1,1′-binaphthol) could have been clarified by the Kobayashi group.[58] According to NMR studies, this complex contains two zirconium centers, two (*R*)-6,6′-dibromo-1,1′-binaphthol molecules, two NMI molecules, as well as one molecule of (*R*)-3,3′-dibrom-1,1′-binaphthol.

3.4.2. The Substrate Range

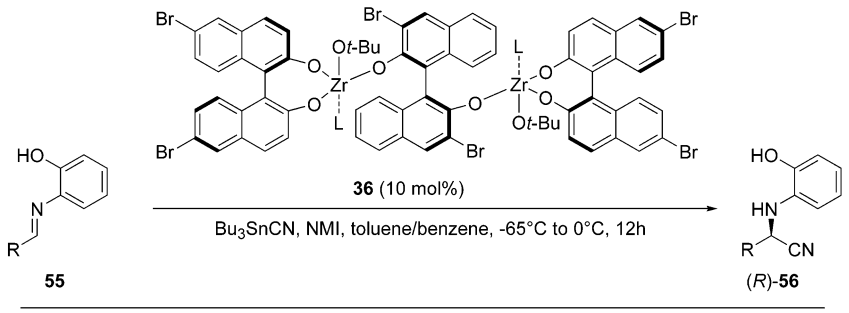
In the presence of 10 mol % of this catalyst **36**, which is very stable, the Strecker reaction was carried out with numerous substrates comprising aromatic as well as aliphatic imines.[58] As a cyanide donor, tributyltin cyanide was used again. The substrate range turned out to be broad, tolerating aromatic as well as aliphatic imines. A selection of examples is shown in Scheme 42. The imines **55a** and

Scheme 41. Structure of the Kobayashi-Type Zirconium Catalyst



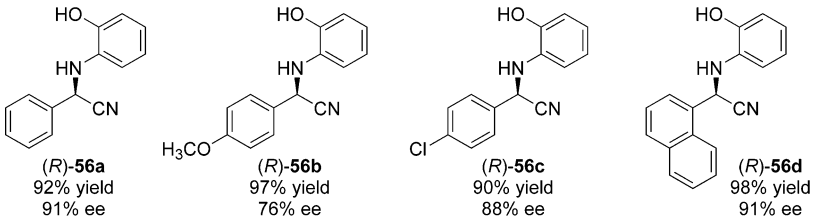
55d, derived from benzaldehyde and 1-naphthaldehyde, gave high enantioselectivities of 91% ee for both products, (*R*)-**56a** and (*R*)-**56d**. The yields were also in an excellent range of 98 and 92%, respectively. In addition, substituted benzaldimines as well as heteroaromatic imines serve as suitable substrates leading to the α-amino nitriles in high 85−97% yields, and with enantioselectivities of up to 92% ee. Notably, also aliphatic imines have been successfully converted into the corresponding α-amino nitrile products.[58] Albeit somewhat lower compared with the

Scheme 42. The Substrate Range of the Kobayashi-Type Zirconium Catalyst



The substrate range (selected examples)

(i) aromatic Strecker products



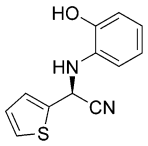
(*R*)-**56a** 92% yield 91% ee

(*R*)-**56b** 97% yield 76% ee

(*R*)-**56c** 90% yield 88% ee

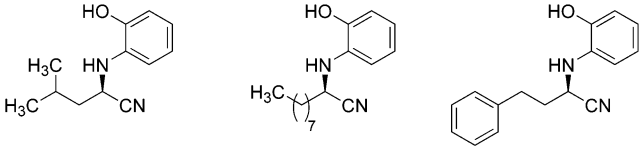
(*R*)-**56d** 98% yield 91% ee

(ii) heteroaromatic Strecker products



(*R*)-**56e** 89% yield 92% ee

(iii) aliphatic Strecker products



(*R*)-**56f** 79% yield 83% ee

(*R*)-**56g** 72% yield 74% ee

(*R*)-**56h** 55% yield 83% ee

aromatic analogues, the enantioselectivities are still in a good range of 74−83% ee.

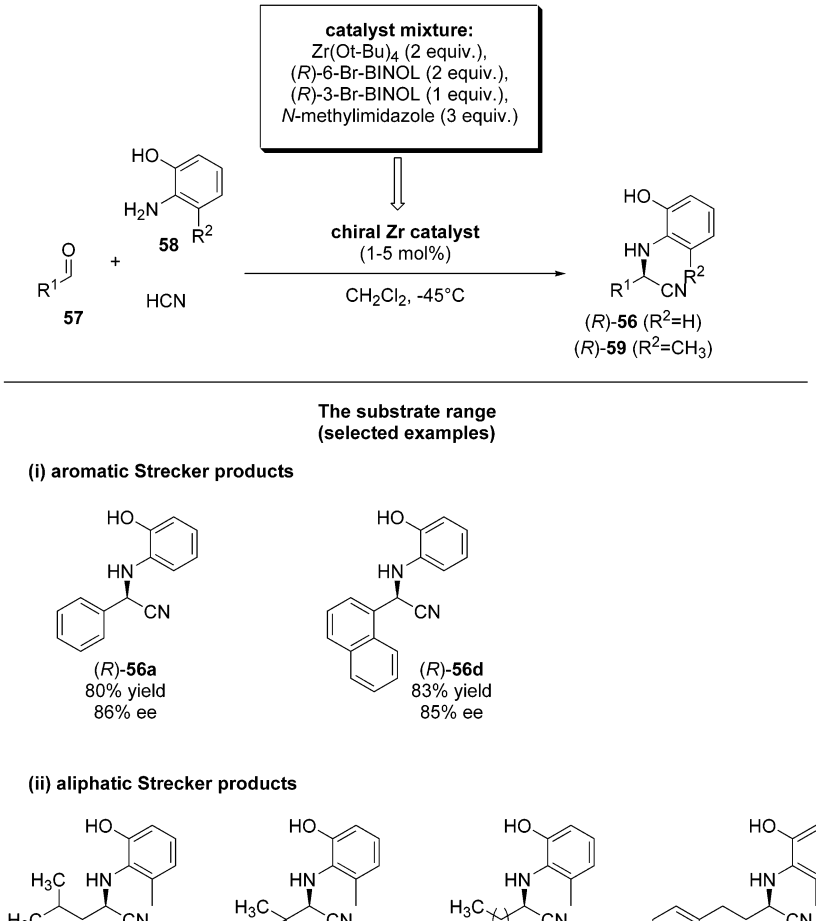
A further synthetic application of the Kobayashi catalyst has been reported recently by Burkhart et al. in a direct asymmetric synthesis of ACPA, which is an intermediate for numerous analogues as drug candidates for neurologic disorders.[62] The asymmetric Strecker synthesis has been integrated in the whole multistep synthesis and is based on the use of the Kobayashi-type zirconium-Br−BINOL catalyst. The desired α-amino nitrile is obtained in high yield and with >90% ee.

The Kobayashi group also focused on the recycling of the bis(tributyl)tin oxide which is formed as a side product from the tributyltin cyanide.[58] The tin oxide could be recovered quantitatively, and reconverted into the cyanide source. In addition, tributyltin cyanide is stable in water. However, there are also some drawbacks using this cyanide source. The price is much higher compared with HCN and TMSCN, and the atom economy is somewhat lower, which is disadvantageous in particular in case of a large scale application. For industrial purposes, the use of HCN as a cheap and in large scale available cyanide source would be more desirable. In addition, the simultaneous use of aldehyde and amine instead of the preformation of an imine would be advantageous.

3.4.3. Strecker Reaction using Amines, Aldehydes, and HCN

Exactly those two aspects have been addressed by the Kobayashi group, too, resulting in the first three-component Strecker synthesis leading to the Strecker products in both high yields, and enantioselectivities.[63] Under optimized conditions, HCN is added to the catalyst at first, followed by addition of this solution to the mixture of aldehyde and amine. The catalyst is prepared from 2 equiv of the Zr(IV) alkoxide, 2 equiv of (*R*)-6,6′-dibromo-1,1′-binaphthol molecules, 1 equiv of (*R*)-3,3′-dibromo-1,1′-binaphthol,

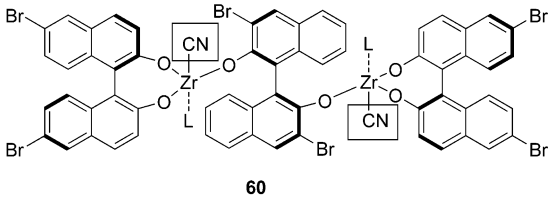
Scheme 43. One-Pot Strecker Synthesis Using Amines, Aldehydes, and HCN



as well as 3 equiv of NMI. The reactions proceed with a catalytic amount of 5 mol % in dichloromethane at −45 °C. A broad range of α-amino nitriles comprising aromatic as well as aliphatic products were formed with enantioselectivities in a high range of 84−94% ee.[63] Selected examples are shown in Scheme 43. In particular, the broad variety of examples with aliphatic aldehydes is noteworthy. Thus, starting from pivaldehyde the α-amino nitrile (*R*)-**59b** was obtained quantitatively with 86% ee (Scheme 43).

Other aliphatic noncyclic amino nitriles can also be prepared very successfully. A yield of 85% and an enantioselectivity of 94% ee was found for the α-amino nitrile (*R*)-**59d**. In general, the yields and enantioselectivities were in the same range when using 2.5 mol % catalytic amount only. As a key catalytic species in this three-component synthesis, the complex **60** has been assumed by the Kobayashi group based on preparative experiments and NMR spectroscopy studies (Scheme 44).[63] Compared to the complex **36**, in the complex **60** the *tert*-butoxy groups are replaced by cyano substituents.

Scheme 44. Structure of the Catalytically Active Species

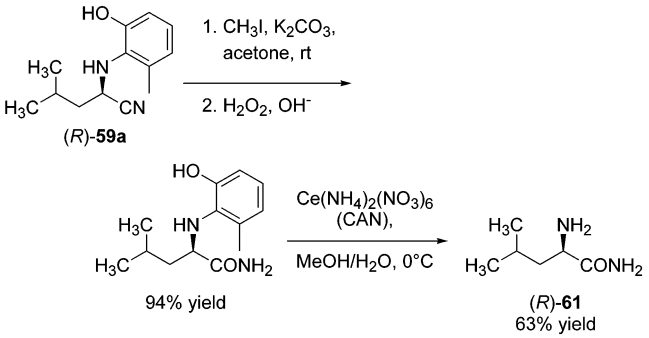


3.4.4 Transformation of α-Amino Nitriles into Amino Acid Amides

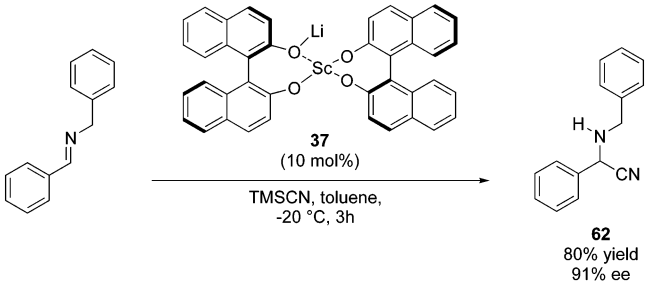
The *N*-substituted α-amino nitriles (*R*)-**59** can be subsequently converted in three steps into the α-amino acid amides. This has been exemplified by the Kobayashi group in the synthesis of D-leucinamide (Scheme 45). This amino acid, (*R*)-**61**, has been obtained in optically pure form in 59% overall yield starting from the α-amino nitrile (*R*)-**59a**.[63]

The *N*-substituent can be removed by cleavage with cerium ammonium nitrate (CAN). However, albeit suitable for lab scale applications, this cleavage method appears to be less favorable for large scale applications. The Kobayashi group also reported further applications in the field of synthesis of α-amino acid derivatives. For example, the preparation of the unnatural α-amino acid D-homophenylalanine has been reported.[63] In addition, an alternative synthesis of D-pipecolic acid methyl ester has been described.

Scheme 45. Transformation of the Amino Nitriles into Amino Acid Amides



Scheme 46. The Strecker Reaction with Vallée-Type Scandium Catalysts



3.5. Chiral Lanthanoid(III) Complexes as a Catalyst

The catalytic power of heterobimetallic lanthanoid catalysts is widely known, and has been impressively demonstrated in particular by the Shibasaki group for a broad variety of asymmetric catalytic syntheses.[36] Recently, new lanthanoid complexes have been developed which are suitable for the Strecker reaction with ketimines.

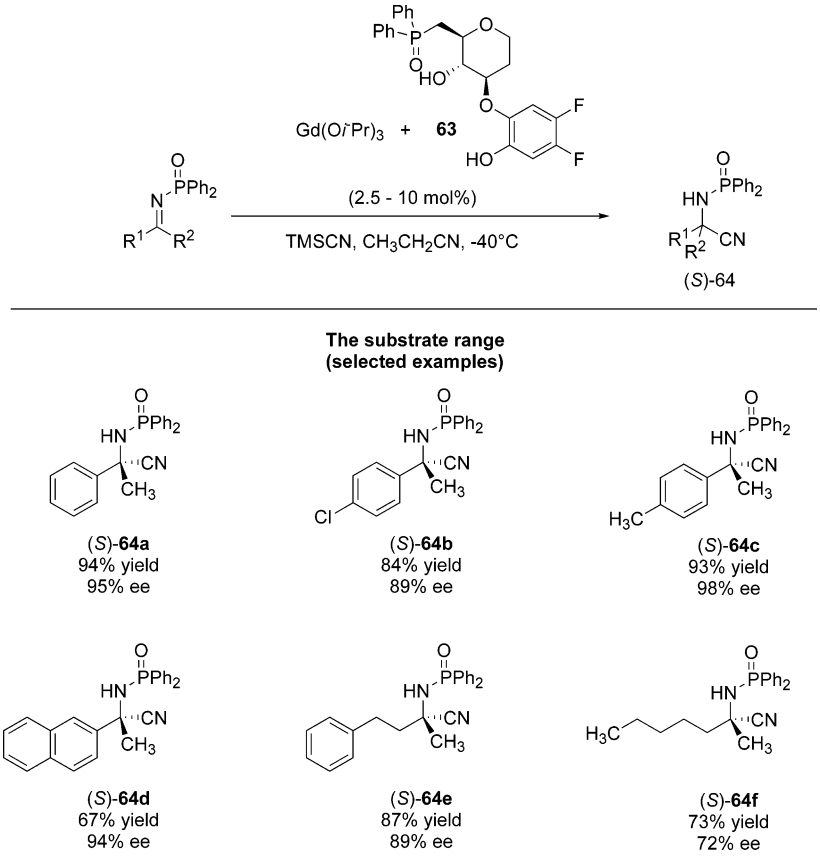
After initial experiments using binaphthol-based aluminum and titanium(III) complexes (which gave less satisfactory results), the Valleé group found that good yields and high enantioselectivities can be obtained when using the heterobimetallic scandium complex, **37**.[64]

As a model reaction, the addition of TMSCN to *N*-benzyl benzaldimine was chosen. In the presence of a catalytic amount of 10 mol % of **37**, a high yield of 80%, and enantioselectivity of 91% ee was obtained after only a 3 h reaction time (Scheme 46). After 9 h, the reaction reached a conversion of >95%. However, the enantiomeric excess was slightly decreased (88% ee), which has been explained by the authors with catalyst poisoning or decay.[64]

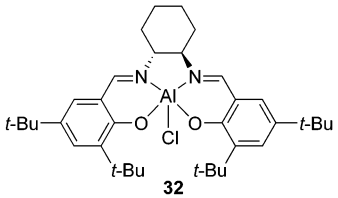
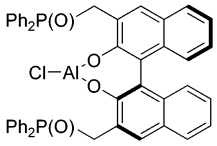
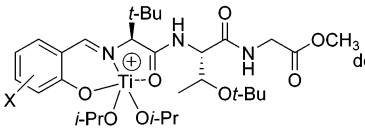
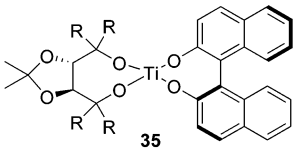
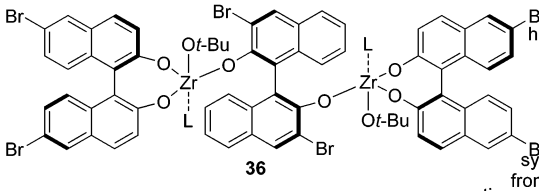
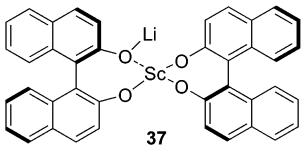
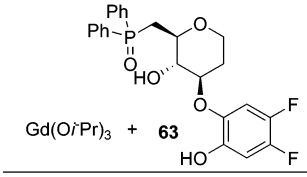
When carrying out this Strecker reaction at −40 °C (at the beginning), HCN can be used as a cyanide source, resulting in decreased enantioselectivities of 81% ee. In addition, a high conversion was observed after 4 h reaction time already. Furthermore, this reaction has also been carried out with a β-naphthyl-derived aldimine and the ketimine derived from acetophenone and benzylamine. In the latter case, however, the enantioselectivities were only modest with ee values in the range of 45−55% ee.[64]

Very recently, Shibasaki and co-workers reported a very efficient lanthanoid catalyst for the Strecker reaction with ketimines.[65] This catalyst which is based on Gd(O*i*-Pr)$_3$ and the carbohydrate-derived

Scheme 47. Shibasaki-Type Strecker Reaction with Ketimines as a Substrate



Scheme 48. Summary of the Strecker Reactions Using Chiral Metal Catalysts

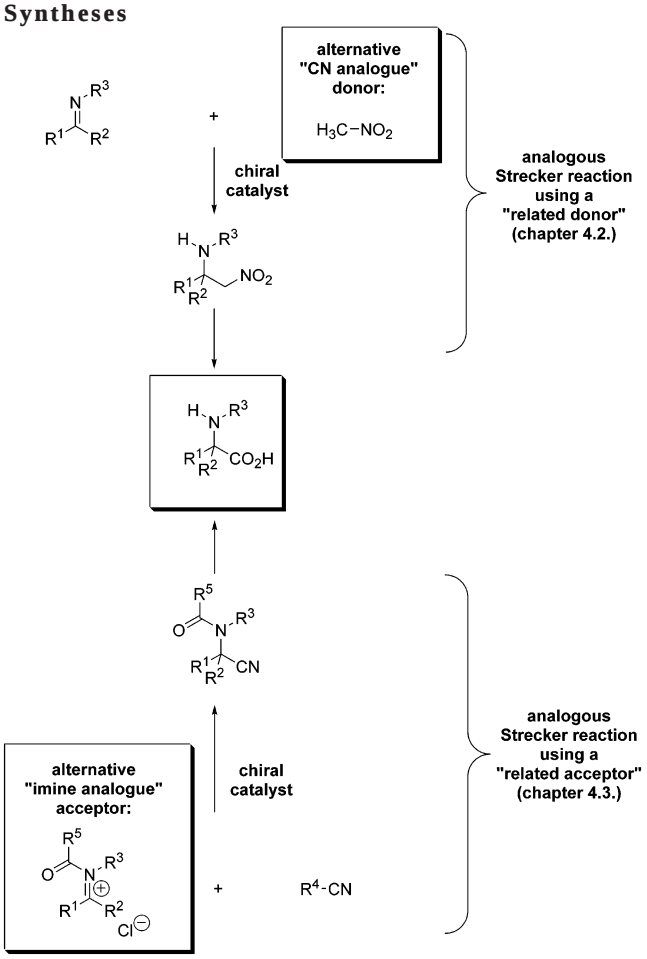
catalyst structure	substrate range	catalytic amount	range of yield [%]	range of ee [%]
 **32**	aromatic aldimines (medium ee for aliphatic aldimines)	5 mol%	91-99	79-95
 **33**	aromatic, heteroaromatic, α,β-unsaturated, aliphatic aldimines	9 mol%	66-97	70-96
 **34**	aromatic, α,β-unsaturated, doubly unsaturated, aliphatic aldimines	2.5-15 mol%	93-100 (conversion)	76-97
 **35** (R=β-naphthyl)	ketimine (one example)	10 mol%	max. 80-95	max. 45-59
 **36**	aromatic, heteroaromatic, aliphatic aldimines; direct one-pot synthesis starting from aldehydes and amines	5-10 mol% 1-5 mol%	55-98 76-100	74-92 84-94
 **37**	aromatic aldimines, ketimine (one example)	10 mol%	max. 80-95 max. 70	86-95 45-55
 $Gd(O^iPr)_3$ + **63**	aromatic, α,β-unsaturated, aliphatic ketimines	2.5-10 mol%	67-99	51-98

ligand, **63**, functions in particular well when using the *N*-phosphinoyl moiety as an *N*-protecting group of the imine (Scheme 47). Notably, the substrate range is very broad, and aliphatic as well as aromatic substrates were accepted. In the presence of a catalytic amount of 2.5−10 mol %, the products of type (*S*)-**64** were obtained with good to high yields of up to 99%, and enantioselectivities of up to 98% ee.[65] In particular, impressive enantioselectivities were obtained using imines derived from acetophenone and *p*-substituted derivatives thereof. For example, in the presence of a catalytic amount of only 2.5 mol %, the product (*S*)-**64c** was obtained in high 93% yield, and with an excellent enantioselectivity of 98% ee. Successful conversions of the products (*S*)-**64** were also done by the Shibasaki group.[65]

3.6. Summary of the Metal-Complex-Catalyzed Enantioselective Strecker Reaction

Recently, several successful metal complex catalysts for the catalytic enantioselective hydrocyanation of imines have been developed. In particular, aluminum-, titanium-, lanthanoid-, and zirconium-based complexes turned out to be highly efficient. The latter type also catalyzes a three-component Strecker reaction starting from an aldehyde, amine, and a cyanide source. The most suitable optically active ligands so far are salen- or binaphthol-type molecules. In gen-

Scheme 49. Overview of Analogous Strecker Syntheses



eral, aromatic imines are good substrates for all of those type of catalysts. In addition, high enantioselectivities have been obtained for aliphatic imines in case of catalysts **33**, **34**, and **36**. Furthermore, an efficient Gd-catalyst has been found for the cyanation of ketimines. An overview about the metal complex catalysts developed so far, and their catalytic efficiency is given in Scheme 48.

Typically, the catalytic asymmetric Strecker reaction with metal complexes as catalysts is carried out with a catalytic amount of 5−15 mol %, but also reduced catalytic amounts in the range of 1−5 mol % often led to excellent results. Thus, in addition to organocatalysts chiral metal complexes represent an interesting and important group of catalysts for the catalytic enantioselective addition of cyanide donors to imines.

4. Analogous Catalytic Enantioselective Strecker Reactions

4.1. Overview

Besides the "classical" type of asymmetric catalytic Strecker reaction, namely, the addition of a cyanide donors to imines, several modified versions have been developed. These methods are based on the use of other donors related to CN which also can be converted into a carboxylic group in a subsequent step, or on the use of acceptors related to imines, e.g., iminium ions. The principles of those two methods are shown in Scheme 49.

Regarding the use of a "cyanide-related" donor which also can be regared as a "carboxylic acid synthon", nitromethane can function as such a molecule. The subsequent conversion of a CH_2NO_2 functionality into a carboxylic acid is well-known in general, and has been also applied for several optically active nitromethane adducts.[66] Thus, the addition of nitromethane is an interesting alternative to the original type of Strecker reaction to prepare α-amino acids due to the potential to convert the CH_2-NO_2 group into a carboxylic acid group.

The second modified Strecker reaction is based on the use of imine-related acceptors. In particular, iminium ions prepared from a quinoline molecule and an acid chloride can function as such imine substitutes. A subsequent addition of HCN would led to the *N*-acylated α-aminonitriles. In this case, a cleavage of the *N*-acyl group is needed in addition to the hydrolysis of the HCN group.

Very recently, for both approaches the first successful asymmetric catalytic examples have been reported which shall be summarized in the following.

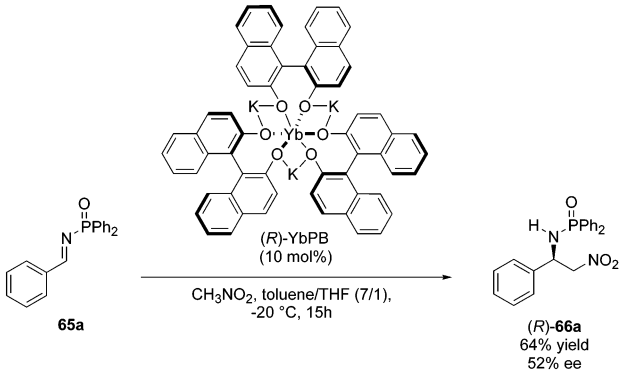
4.2. Analogous Strecker Reactions /1: The Use of CN Analogue Donors

The first example of a catalytic asymmetric addition of nitromethane to imines, the so-called nitro-Mannich reaction, has been reported by the Shibasaki group in 1998.[67,68] The resulting *β*-nitroamine products are versatile intermediates for the synthesis of α-amino acids (by hydrolysis), and diamines. Applications of the nitro-Mannich reaction, and/or related reactions with other nitroalkanes have also been developed by the Shibasaki group and Jorgensen group.[69,70] Although nitroalkane-adducts derived from other nitroalkanes than nitromethane cannot be converted into the corresponding α-amino acids due to the additional substituent at the α-nitro position, these *β*-nitroamines are versatile precursors for the synthesis of diamines bearing two stereogenic centers.

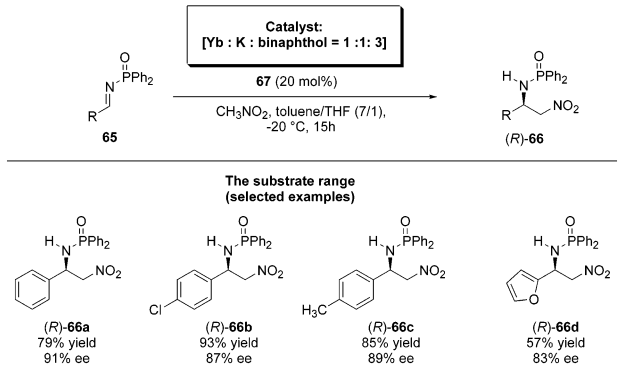
In the presence of heterobimetallic catalysts, the addition of nitromethane to imines was not successful when using *N*-benzyl imines.[67] However, a remarkable improvement was made when applying *N*-phosphinoyl imines of type **65** (e.g., model substrate **65a**) as a substrate. The phosphinoyl group as an *N*-substituent of the imine was chosen since in previous studies[71] an interaction of a P═O double bond with a heterobimetallic lanthanoid complex was found. On the basis of these findings, the Shibasaki group supposed that a comparable effect could lead to a coordination of phosphinoyl imines to the lanthanoid catalyst resulting in an asymmetric induction for the desired reaction. In a first screening for a suitable catalyst, the heterobimetallic complex YbPB which consists of an ytterbium center ion, three potassium ions, and three molecules of binaphthol (this catalyst was also the most efficient catalyst in the previously reported asymmetric catalytic hydrophosphonylation of cyclic imines; see ref 71) gave the best results with 64% yield, and 52% ee for the product (*R*)-**66a** (Scheme 50).

An improvement of the moderate enantioselectivity was achieved when decreasing the amount of potas-

Scheme 50. (R)-YbPB-Catalyzed Addition of Nitromethane to Imines



Scheme 51. Shibasaki-Type Nitro-Mannich Reaction



sium in the heterobimetallic complex. Thus, for the synthesis of (*R*)-**66a** a yield of 79%, and an enantioselectivity of 91% ee was observed in the presence of a heterobimetallic catalyst **67** with a molecular ratio of ytterbium/potassium/binaphthol of 1:1:3.[67] Slow addition of nitromethane was a further prerequisite for high enantioselectivity. The scope and limitation of this new synthesis has been investigated revealing that a broad range of substituted aromatic aldimines, e.g., **65a**,**b**, as well as heteroaromatic substrates, e.g., **65d**, bearing an *N*-phosphinoyl substituent can be converted successfully. For the corresponding nitro-Mannich adducts (*R*)-**66** moderate to high yields of up to 93%, and enantioselectivities in the range of 69−91% ee were obtained (Scheme 51).

To clarify the catalyst structure of **67**, mass spectrometrical investigations of the catalyst solution were carried out. Accordingly, an aggregated complex consisting of YbK(binaphthoxide)$_2$] and binaphthol which are coordinated by means of Lewis acid-Lewis base interactions and hydrogen bonding has been suggested as the catalytically active species.[67]

So far, the nitro-Mannich adducts (*R*)-**66** have been used only for the preparation of corresponding diamines via reduction of the nitro-group.[67] However, due to the proven potential of converting CH_2NO_2 groups into a carboxylic acid functionality (for an example, see refs 66 and 68), an access to the corresponding α-amino acids according to Scheme 49 should be also possible.

4.3. Analogous Strecker Reactions /2: Reissert Type Reactions

4.3.1. The Catalytic Concept

The Reissert reaction is a further reaction related to the Strecker synthesis, and heterocyclic α-amino acids can be obtained as final products. In this reaction, which was discovered in 1905 by Reissert,[72] cyanide reacts with quinoline in the presence of benzoyl chloride under formation of the corresponding *N*-benzoyl α-amino nitrile. However, in the Reissert reaction the cyanide does not add to an imine (as in the Strecker reaction), but to the *N*-acyl quinolinium ion which is formed by the reaction of quinoline **67a** and the acid chloride. Nevertheless, since the reaction consists of the use of cyanide and an imine-related iminium ion, and since the products which are obtained are also α-amino nitrile derivatives, the catalytic asymmetric version of the Reissert reactions shall be summarized in the following as an "analogous Strecker reaction". The concept of this type of heterocyclic amino acid synthesis is also shown above in Scheme 49.

For the first time, an asymmetric Reissert-type reaction has been reported by Shibasaki and coworkers using the bifunctional and monometallic complex **68** as an optimized catalyst (Scheme 52).[73,74] Screening a variety of acid halides for the Reissert reaction with quinoline **67a** and TMSCN showed that electron-rich acyl chlorides, in particular, benzoyl chloride and 2-furoyl chloride, led to the highest enantioselectivities of 83 and 85% ee, respectively. A mixture of toluene and dichloromethane turned out to represent the preferred solvent. For other substrates, the use of dichloromethane only gave high enantioselectivities.

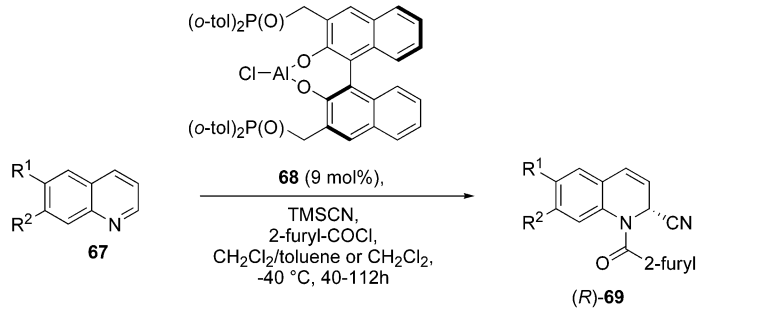
4.3.2. The Substrate Range

On the basis of the optimized reaction conditions, the substrate range has been investigated with numerous quinolines.[73,74] Using a catalytic amount of 9 mol % of **68**, the desired *N*-acylated Reissert-products (*R*)-**69** have been obtained with good enantioselectivities of up to 91% ee, and in up to nearly quantitative yields.[73,74] Representative examples are given in Scheme 52.

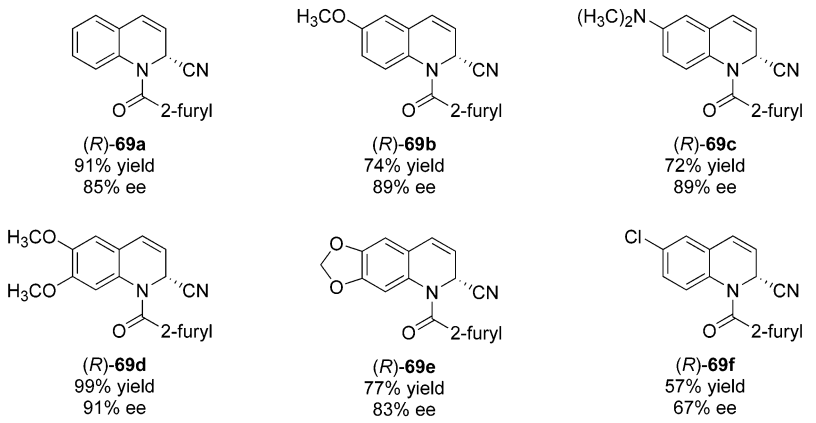
For example, the dimethoxy-substituted quinoline, **67d**, was converted into the corresponding *N*-acyl amino nitrile (*R*)-**69d** in 99% yield, and with 91% ee. The asymmetric Reissert reaction has been successfully extended to the use of isoquinoline **70**.[73,74] In the presence of **33** as a catalyst, an enantioselectivity of 71% ee accompanied by 99% yield were observed for the isoquinoline derivative (*R*)-**71** (Scheme 53).

The Shibasaki group successfully extended the asymmetric Reissert reaction toward the construction of *N*-acyl amino nitriles bearing a quaternary stereocenter.[75] The resulting products of type **74** were obtained with enantioselectivities of up to 98% ee. For example, in the presence of only 2.5 mol % of the catalyst **73** the Reissert product (*R*)-**74** was obtained in 62% yield, and with excellent 95% ee (Scheme 54). This product represents a versatile intermediate for the potent anticonvulsant MK801.[75]

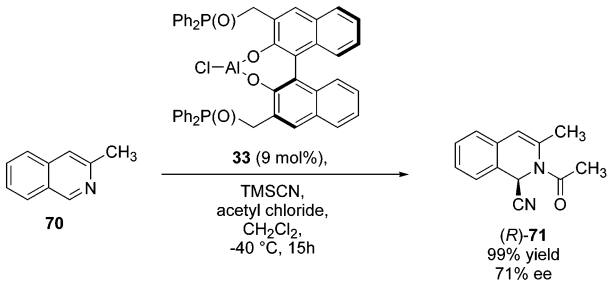
Scheme 52. Shibasaki-Type Reissert Reaction



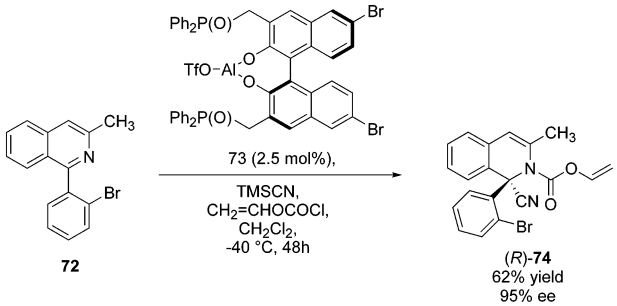
The substrate range (selected examples)



Scheme 53. Reaction with Isoquinoline as a Substrate



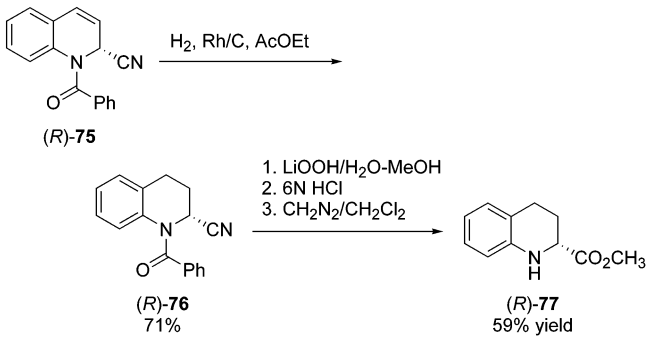
Scheme 54. Synthesis of *N*-Acyl Amino Nitriles Bearing a Quaternary Stereocenter



4.3.3. Transformation of N-Acyl Aminonitriles into α-Amino Acids

The Reissert products can be converted very efficiently into the corresponding nonacylated α-amino acids. This has been exemplified in the synthesis of methyl tetrahydroquinoline-2-carboxylate, which is a pharmacophore of the glycine-site antagonist of a

Scheme 55. Transformation of the Chiral Reissert Products into α-Amino Acids



NMDA receptor on neurons.[73,74] Starting from the α-amino nitrile (*R*)-**75**, hydrogenation and subsequent hydrolysis of the cyano group and amide cleavage proceeds well furnishing the desired heterocyclic α-amino acid ester (*R*)-**77** without any loss of enantiomeric purity (Scheme 55).

4.3.4. Application for Pharma Intermediate

The asymmetric catalytic Reissert reaction has been also successfully applied as a key step in a 10-step synthesis of Merck's potent NMDA receptor antagonist (−)-L-689,560 which represents a promising drug candidate for Alzheimer's disease.[74] For this purpose, a Reissert adduct (related to **69**) which is based on the use of a quinoline with three substituents was prepared with high 96% ee.

4.3.5. Reaction Mechanism

A reaction mechanism which has been additionally supported by kinetic studies was also proposed by the

Shibasaki group.[74] Accordingly, the reaction is promoted by a dual activation of the iminium ion and TMSCN by the Lewis acid−Lewis base catalyst of type **33**. In the transition state, the iminium ion is bound to the aluminum catalyst via a coordination of the amide oxygen (of the *N*-acyl group) to the alumium center metal. In addition, TMSCN is activated by coordination to the phosphinoyl moiety of the catalyst **33**. Due to the corresponding efficient dual activation of both substrates, the subsequent addition of cyanide proceeds in a highly enantioselective manner.

5. Summary and Outlook

In conclusion, great achievements have been made recently in the organocatalytic and metal-catalytic asymmetric hydrocyanation of imines. Several already highly efficient asymmetric methods are now available for the catalytic enantioselective Strecker reaction. Besides excellent enantioselectivities, the low catalytic amount of several type of developed catalysts are particularly noteworthy. The variety of catalysts also indicates a high potential for further successful Strecker reaction applications in the future. In addition, several "analogous syntheses" which are based on the use of either other type of donors or imine-related acceptors have been developed. Those approaches also give optically active α-amino acids after further conversion.

Among future challenges will be further developments of a direct access to the Strecker products starting from aldehyde, amine, and a cyanide donor. Thus, the isolation of the preformed imine could be avoided leading to the desired α-amino nitriles and acids, respectively, directly in a three-component, one-pot reaction. From an industrial point of view, catalyst recovery, immobilization, and further optimized transformations into α-amino acids are among the major goals in the future.

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