

CHAPTER 1

THE CATALYTIC ASYMMETRIC STRECKER REACTION

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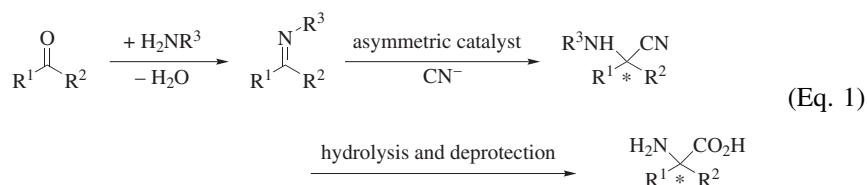
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INTRODUCTION

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



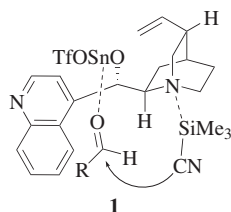
The catalytic promotion and enantiocontrol of cyanide addition to imines is the main focus of the catalytic asymmetric Strecker reaction. Therefore, isolated and purified imines are normally used as substrates. The catalyst turnover efficiency and enantioselectivity of this step are intimately related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

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

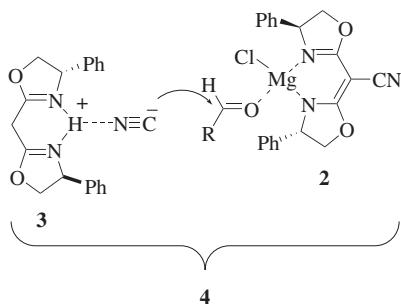
MECHANISM AND STEREOCHEMISTRY

Many of the catalysts for the asymmetric Strecker reaction (and the Reissert reaction) appear to promote the reaction through dual activation¹²⁻¹⁵ of the

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

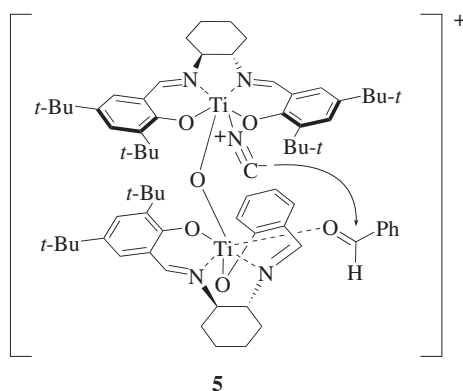


A synergistic combination catalyst was reported for an enantioselective cyanosilylation of aldehydes. Magnesium bisoxazoline **2** acted as a chiral Lewis acid to activate the aldehyde, and uncomplexed bisoxazoline **3** as a Brønsted base to activate HCN as shown in complex **4**.¹⁸ HCN was generated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



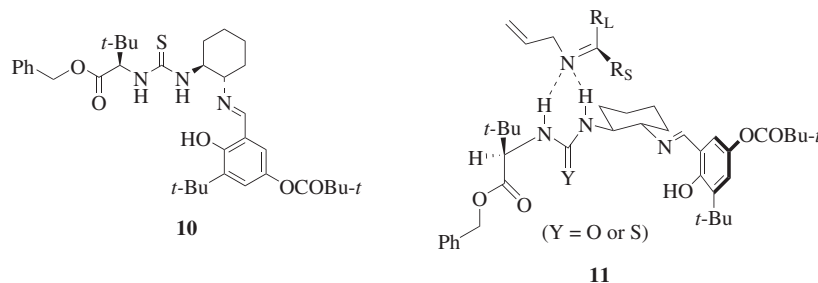
Extensive mechanistic studies of an asymmetric cyanosilylation of aldehydes and ketones catalyzed by a salen–titanium complex revealed that the actual catalyst is a bimetallic complex bridged by a μ -oxo atom (**5**).^{19,20} One titanium atom acts as a Lewis acid to activate the substrate, while the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

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

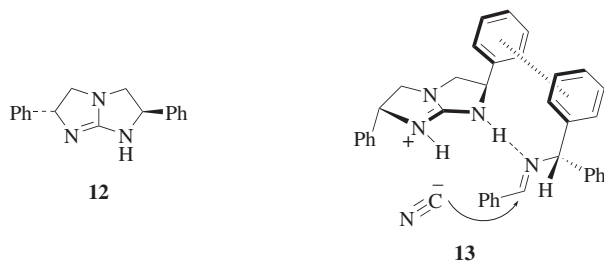


Asymmetric catalyst **6** (prepared from Et_2AlCl and the corresponding BINOL-derived ligand) promotes cyanosilylation of aromatic and aliphatic aldehydes with excellent enantioselectivities (Eq. 2).^{23,24} This catalysis is believed to occur via a dual activation mechanism, in which the aluminum provides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

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

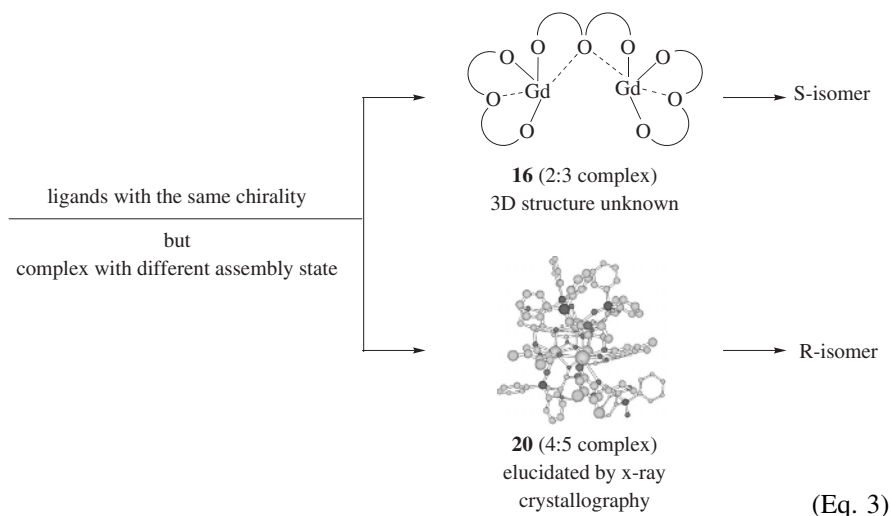


The other useful organocatalyst for the Strecker reaction is the chiral C-2-symmetric bicyclic guanidine catalyst **12**.³⁷ This catalyst was proposed to promote the Strecker reaction through a dual activation mechanism as shown in intermediate **13**. The nucleophile HCN is deprotonated by the basic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



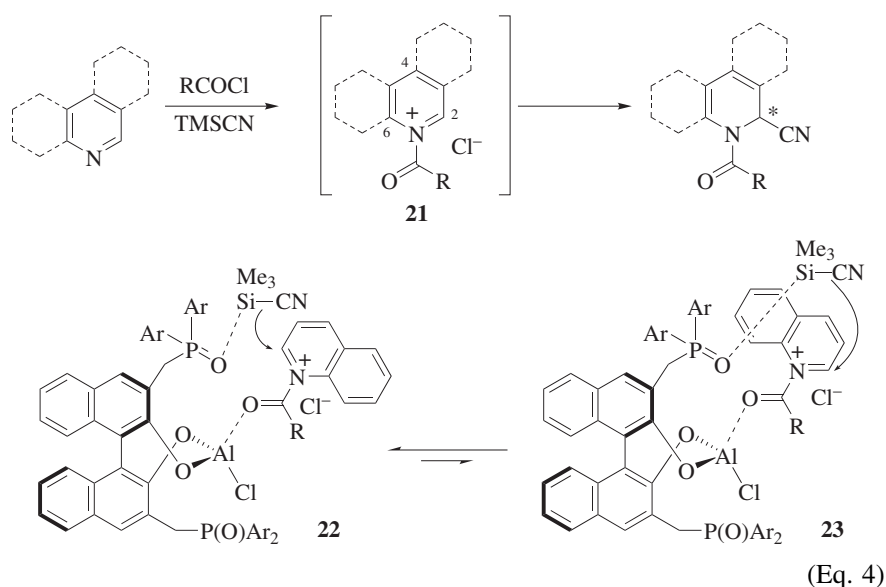
to **18** through protonolysis by HCN did not occur, and no reaction proceeded in the absence of a catalytic amount of TMSCN. When HCN was used as the additive in combination with a catalytic amount of TMSCN, TMSCN was regenerated at the protonolysis step (**17** to **18**). Therefore, only a catalytic amount of TMSCN (and a stoichiometric amount of HCN) is required. Labeling studies using TMS^{13}CN and kinetic studies revealed that the actual nucleophile is not TMSCN, but rather the gadolinium cyanide generated through transmetalation from TMSCN.⁴²

A catalytically active species was crystallized and its structure was elucidated by X-ray crystallography using the dichlorocatechol-containing ligand **15**.⁴³ The crystal, however, was not the 2:3 complex **16** (active catalyst prepared in situ), but a 4:5 complex (**20**) of gadolinium and **15**. Although both polymetallic complexes contain the chiral ligands with the same absolute configuration, crystal **20** (4:5 complex) produced the enantiomers of the Strecker products compared to those obtained by using the in situ prepared 2:3 complex (**16**) (Eq. 3). These results demonstrated the importance of the higher order assembly structure of the polymetallic asymmetric catalyst for its function. Due to the structural complexity of the catalysts, three-dimensional models for enantioinduction have yet to be clarified.



The Reissert reaction⁴⁴ is an acyl cyanation of *N*-heteroaromatic compounds using a combination of an acylating reagent (such as acyl halide or halo carbonate) and a cyanating reagent (such as TMSCN or NaCN). This reaction is very important for the synthesis of biologically active compounds containing *N*-heterocycles.^{45,46} The reaction proceeds through an initial *N*-acylation followed by a dearomatizing cyanation (Eq. 4). Because the amide bond of the *N*-acylated heteroaromatic intermediates **21** (such as acylquinoliniums, acylisoquinoliniums, and acylpyridiniums) are conformationally flexible, it is essential to define the positions of both the electrophile and the nucleophile by the asymmetric

catalyst to realize high enantioselectivity. All the reported catalytic enantioselective Reissert reactions^{47–50} to date have utilized Lewis acid–Lewis base bifunctional aluminum complexes similar to **6** as the catalysts. In a typical proposed transition-state model (**22**), the *N*-acylquinolinium intermediate is activated by the aluminum, and the TMS-CN is activated by the phosphine oxide of the catalyst. Due to steric factors, the reaction via the *s*-trans *N*-acylquinolinium **22** should be more favorable than that via the *s*-cis isomer **23**. Thus, the reactive conformer with regard to the amide bond is influenced by the asymmetric catalyst.



The catalytic enantioselective Reissert reaction of pyridine derivatives presents additional difficulties. There are three similarly electrophilic carbon centers on the acyl pyridinium intermediate (C-2, 4, and 6 of **21**). Therefore, an asymmetric catalyst needs to facilitate one specific pathway out of a possible six (three positions \times two faces) to produce one specific regioisomer with high enantioselectivity. As will be discussed below, a finely tuned bifunctional asymmetric catalyst is able to elegantly solve this problem.⁵⁰

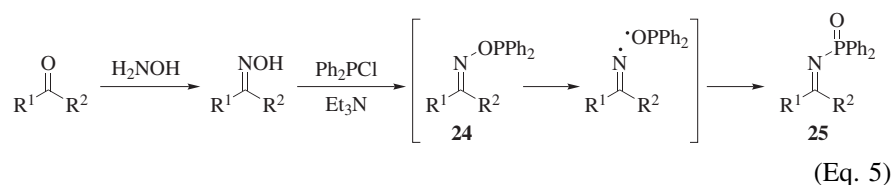
SCOPE AND LIMITATIONS

Imine Synthesis

There are mainly two types of imines that have been utilized in catalytic enantioselective Strecker reactions: (1) simple amine-derived imines such as *N*-allyl, *N*-benzyl, *N*-benzhydryl, and *N*-fluorenyl imines, and (2) activated imines containing electron-withdrawing groups on the nitrogen atom, such as *N*-phosphinoyl and sulfonyl imines. Simple amine-derived aldimines are the most readily prepared by mixing the aldehydes and amines in the presence of desiccant. Many of

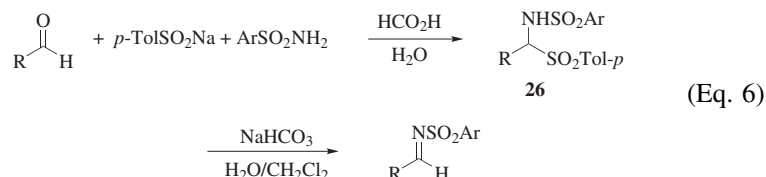
these simple amine-derived imines are labile to purification using silica gel column chromatography or during distillation at high temperature; therefore, imines purified by recrystallization are preferred. The substrate purity is generally very important for catalytic enantioselective reactions, because trace amounts of impurities might have detrimental effects on the asymmetric catalyst. There is, however, an example of using in situ-generated aldimines as substrates for the catalytic enantioselective Strecker reaction (see the chiral Zr-catalyzed three-component reaction).⁵¹

On the other hand, *N*-phosphinoyl imines and *N*-sulfonyl imines require multistep syntheses from the corresponding aldehydes or ketones. Although *N*-phosphinoyl aldimines have not been utilized as substrates for the catalytic asymmetric Strecker reaction, *N*-phosphinoyl ketimines are excellent substrates.^{39–43} *N*-Phosphinoyl ketimines can be synthesized in two steps from the corresponding ketones (Eq. 5)⁵² via oxime formation followed by treatment with R₂PCl. The reaction of ketoximes with R₂PCl at low temperature produces unstable *O*-phosphinoyl oximes **24** as the initial products, which undergo rearrangement to give *N*-phosphinoyl imines **25** at higher temperature through a radical-cage mechanism.^{53,54} Interestingly, *E/Z* geometrical isomerization of phosphinoyl ketimines is very fast even at low temperature based on NMR studies.³⁹ This characteristic is important for the induction of high enantioselectivity from substrates having a wide variety of substituents, because imine geometrical isomers (with regard to the C=N bond geometry) produce enantiomeric products. The cyanation should proceed from the more reactive imine geometry, and so the thermodynamic stability of (*E*) and (*Z*) *N*-phosphinoyl imines (*E/Z* ratio of imines) is not related to the enantioselectivity. Although *N*-phosphinoyl imines are more electrophilic than simple amine-derived imines, they are generally quite stable to silica gel purification. In addition, many of the aromatic ketone-derived phosphinoyl imines are crystalline.



N-Sulfonylimines are the most activated (electron-deficient) imines. *N*-Sulfonylimines derived from aromatic aldehydes or aliphatic aldehydes bearing no enolizable α -protons are relatively easy to prepare. For example, condensation of an aldehyde with a sulfonamide in the presence of a Lewis acid (e.g. TiCl₄, BF₃•OEt₂, (EtO)₄Si)^{55,56} or a Brønsted acid (e.g. *p*-TsOH, amberlyst-H⁺, HCO₂H)⁵⁷ affords the target imines. Aliphatic *N*-sulfonyl aldimines have been prepared in situ without purification in two steps (Eq. 6):⁵⁸ (1) condensation of an aldehyde, an arenesulfonic acid sodium salt, and a sulfonamide in the presence of formic acid and water to form the corresponding sulfonamide sulfone **26**, then (2) treatment of the isolated sulfone with a mild base such as sodium bicarbonate.

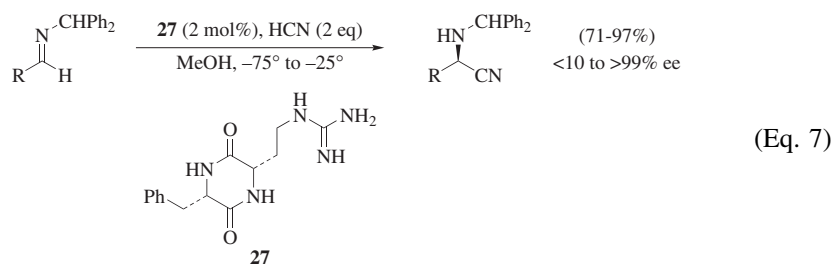
Due to their lability, the aliphatic *N*-sulfonylimines are used in further reactions without purification.



Catalytic Enantioselective Strecker Reaction of Aldimines

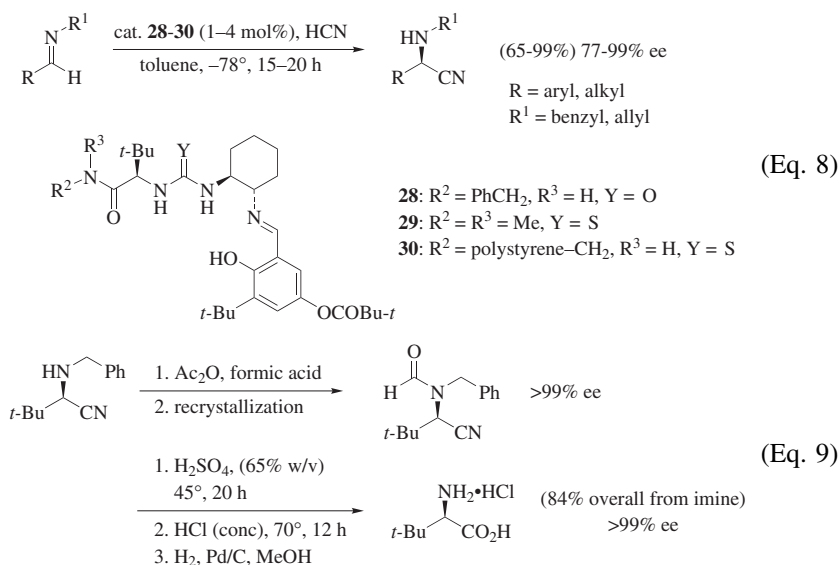
The catalytic enantioselective Strecker reaction of aldimines can be categorized into two classes: (1) reactions promoted by chiral organocatalysts and (2) reactions promoted by chiral metal catalysts.

Enantioselective Strecker Reaction of Aldimines Catalyzed by Chiral Organocatalysts. The first example of a catalytic enantioselective Strecker reaction was reported using organocatalyst **27**,⁵⁹ which was developed based on the structure of a previously reported asymmetric catalyst that promotes cyanosilylation of aldehydes.^{60–63} Catalyst **27**, containing guanidine and (*S*)-phenylalanine moieties, can promote Strecker reactions of aromatic aldimines with high to excellent enantioselectivity (Eq. 7). Heteroaromatic and aliphatic imines afforded products with only low enantioselectivities (up to 32% ee). The products can be converted to optically active α -amino acids via a one-step acid hydrolysis.

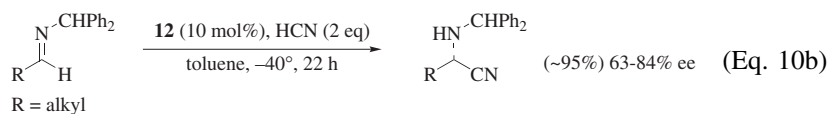
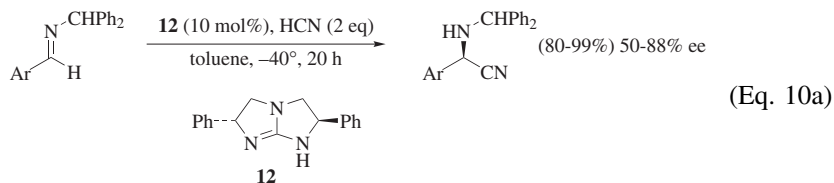


A more general asymmetric organocatalyst class for the Strecker reaction was developed using urea or thiourea as the activating moiety of imines, giving thiourea catalysts **28–30**. Optimization of each structural module of the catalyst by a combinatorial approach led to the identification of catalysts that produce excellent enantioselectivity and catalyst activity with a wide range of aldimines containing aromatic and aliphatic substituents (Eq. 8).^{32,33} The enantioselectivity is not affected by the size of the nitrogen protecting group, and allylamine-derived and benzylamine-derived imines produced comparable enantioselectivity. This tendency can be explained based on model **11**. Resin-bound asymmetric catalyst **30** is as effective as the soluble catalysts **28** and **29**. Additional advantages of using

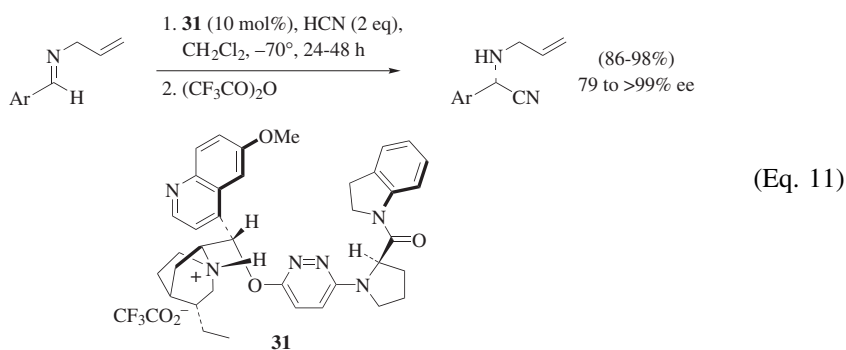
catalyst **30** are facile catalyst recovery and product isolation by simple filtration. The filtered catalyst was reusable for at least ten cycles without any loss of enantioselectivity or catalyst activity. The products were converted to enantiomerically pure α -amino acids through protection of the nitrogen atom with a formyl group, recrystallization, nitrile hydrolysis to a carboxylic acid, deformylation, and removal of the *N*-benzyl group. A typical conversion process is shown in Eq. 9.



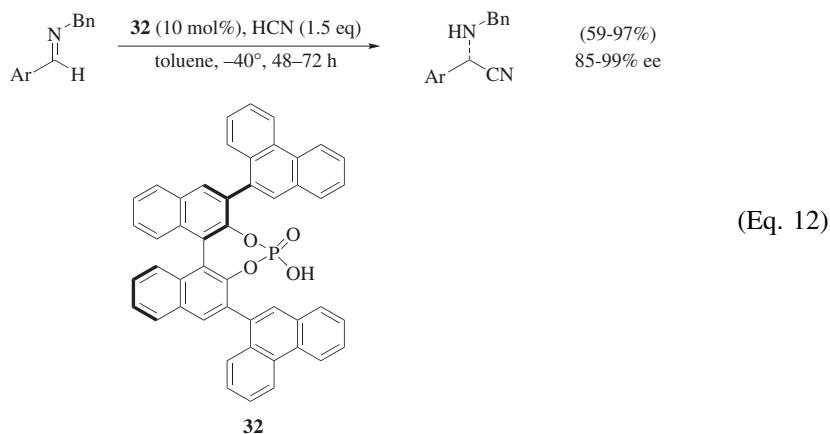
Although substrate generality is not as broad as for the thiourea catalysts **28–30**, chiral C-2-symmetric guanidine **12** is a simple yet highly enantioselective organocatalyst for the Strecker reaction of *N*-benzhydryl aldimines.³⁷ The sterically bulky *N*-benzhydryl group is essential for high enantioselectivity. Aromatic aldimines produced high enantioselectivity, while aliphatic aldimines produced less satisfactory results (Eqs. 10a & 10b). The enantioselectivity reversed depending on the substrates, with aromatic imines affording products in the R-configuration and aliphatic imines affording S-configurational products. The absolute configuration of the products from aromatic ketimines can be explained using model **13**.



Chiral ammonium salt **31** is an effective catalyst for the asymmetric Strecker reaction of *N*-allyl aromatic aldimines (Eq. 11).⁶⁴ The reaction was proposed to proceed through the attack of cyanide on the imine, which is activated by hydrogen bond formation to the ammonium proton of the catalyst. The reaction should occur in the U-shaped pocket constructed by the three aromatic groups of the catalyst. Bulky substrates containing *N*-benzyl or *N*-benzhydryl protecting groups produced less satisfactory enantioselectivities. In addition, aliphatic aldimines were poor substrates in this reaction.

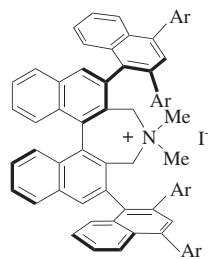
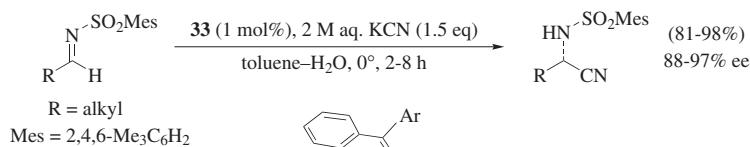


BINOL-derived chiral phosphates are versatile Brønsted acid organocatalysts.^{65,66} A highly enantioselective catalytic Strecker reaction was reported using catalyst **32** (Eq. 12).⁶⁷ Only aromatic imines produced high enantioselectivities. The activation of the substrate aldimine occurs in the chiral environment through protonation by the phosphate.



Chiral quaternary ammonium salt **33** is a useful asymmetric phase-transfer catalyst for the Strecker reaction of aliphatic *N*-sulfonyl aldimines (Eq. 13).⁶⁸ Inexpensive and easy-to-handle KCN can be used as a cyanide source. Generally, enantioinduction from aliphatic aldimines is more difficult than from aromatic

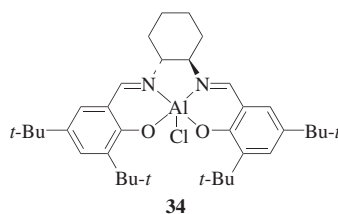
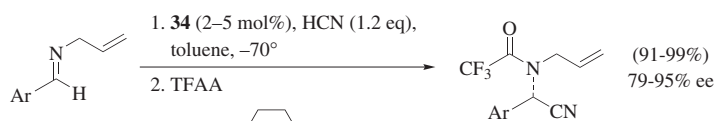
aldimines. This phase-transfer-catalyzed reaction, however, is notable because aliphatic aldimines produced better results than aromatic aldimines.



33: Ar = 4-CF₃C₆H₄

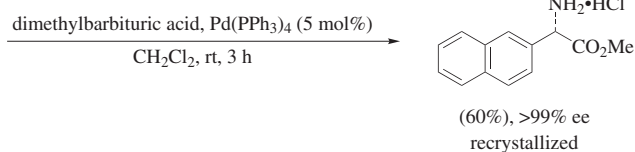
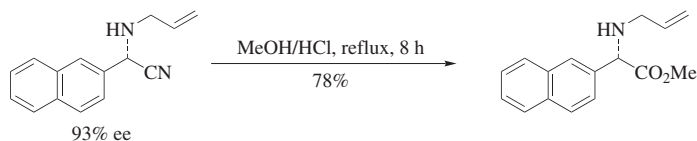
(Eq. 13)

Enantioselective Strecker Reaction of Aldimines Catalyzed by Chiral Metal Complexes. The (salen)aluminum(III) complex **34** is an excellent catalyst for the enantioselective Strecker reaction between aromatic aldimines and HCN (Eq. 14).⁶⁹ Aliphatic imines afford products with moderate enantioselectivities (37–57% ee). The reaction is best performed at very low temperature (-70°) to avoid competing background reactions. Catalyst **34** is easily prepared on a large scale and appears to have an indefinite shelf-life even when stored under ambient conditions.⁷⁰ The products can be converted to enantiomerically pure α -amino esters through methanolysis of the cyanide followed by *N*-deprotection (Eq. 15).



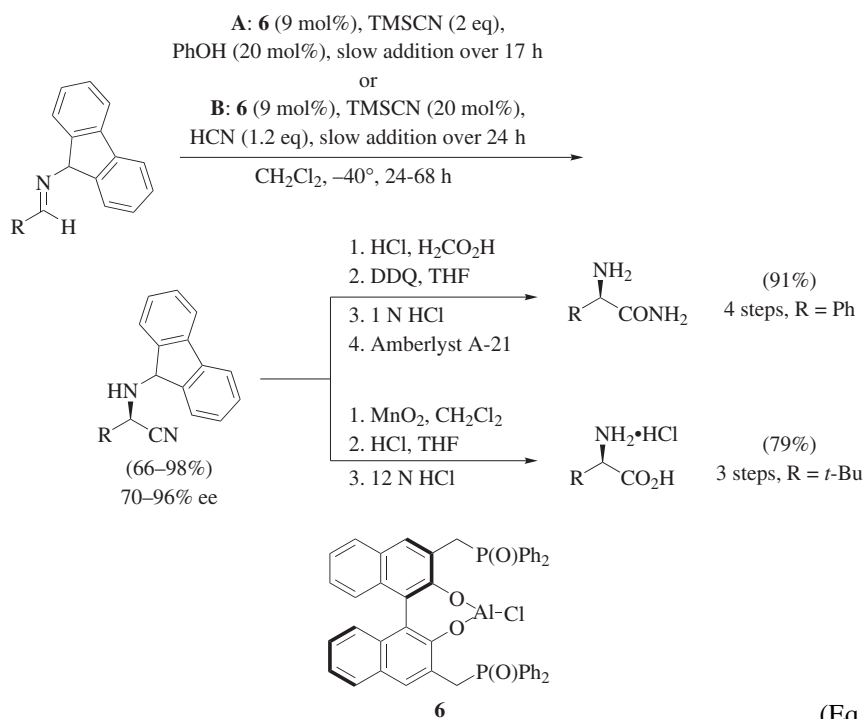
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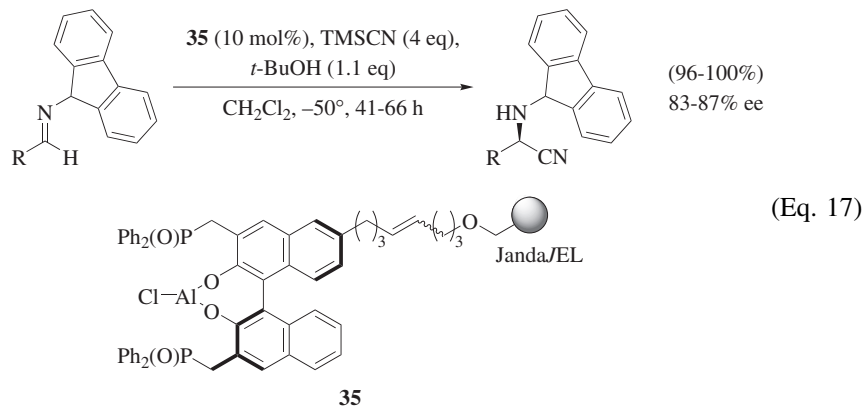
(Eq. 14)



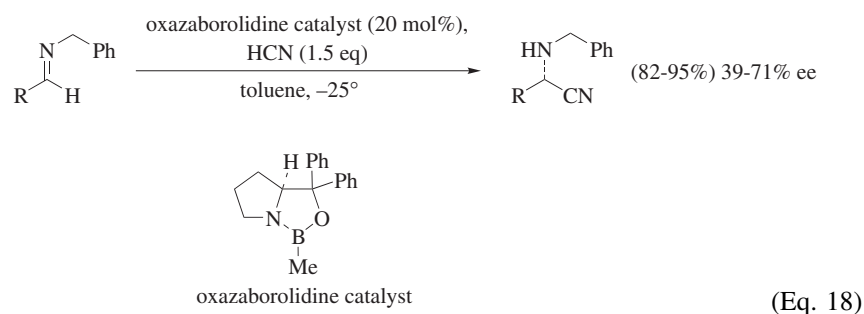
(Eq. 15)

Asymmetric bifunctional catalyst **6** was developed as a general catalyst for the Strecker reaction of aldimines, and high enantioselectivities have been observed using this catalyst with both aromatic and aliphatic substrates.^{26,27} Catalyst **6** acts in a bifunctional manner: aluminum activates the imine as a Lewis acid, and the phosphine oxide activates TMSCN as a Lewis base (**8** in Eq. 2).⁷¹ The *N*-protecting group of the substrate has a large effect on the enantioselectivity, and *N*-fluorenylimines gave optimal results. Slow addition of a catalytic amount (20 mol%) of phenol into the reaction mixture containing a stoichiometric amount of TMSCN dramatically increased the reaction rate (condition A), and the reaction was completed in less than 68 hours. Alternatively, a more atom-economic combination of a catalytic amount of TMSCN and a stoichiometric amount of HCN can be used (condition B). Both conditions produced comparable enantioselectivity. The *N*-fluorenyl group of the product could be removed through oxidative treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or manganese dioxide to generate the corresponding fluorenone-derived imine, followed by acidic hydrolysis (Eq. 16). A recyclable, solid-supported asymmetric catalyst **35** was developed by connecting catalyst **6** to Janda/JEL⁷² (Eq. 17).⁷³ Catalyst **35** produced slightly lower enantioselectivity than the soluble catalyst **6**, and the catalyst activity decreased significantly after the fourth recycle.

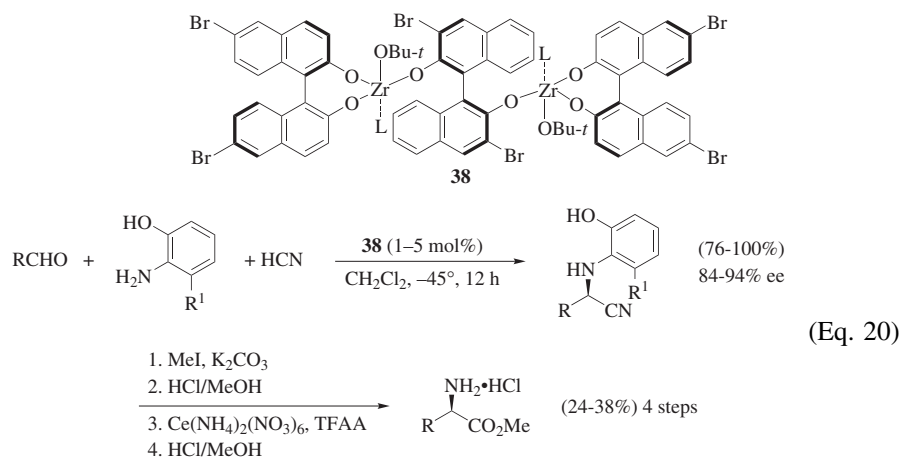
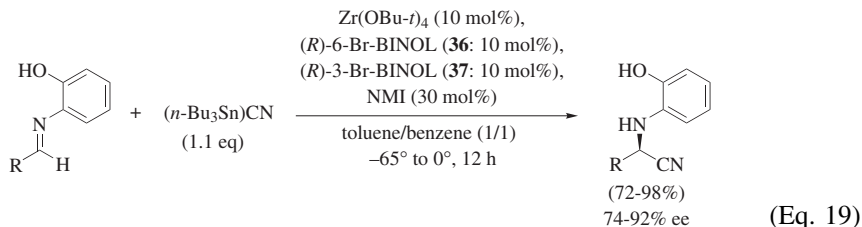




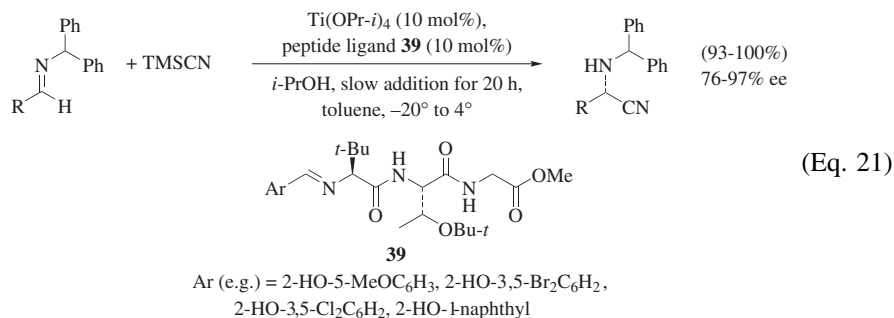
Corey's oxazaborolidine¹⁴ catalyst was utilized in the catalytic enantioselective Strecker reaction of aldimines. Enantioselectivity was, however, only moderate (up to 71% ee, Eq. 18).⁷⁴



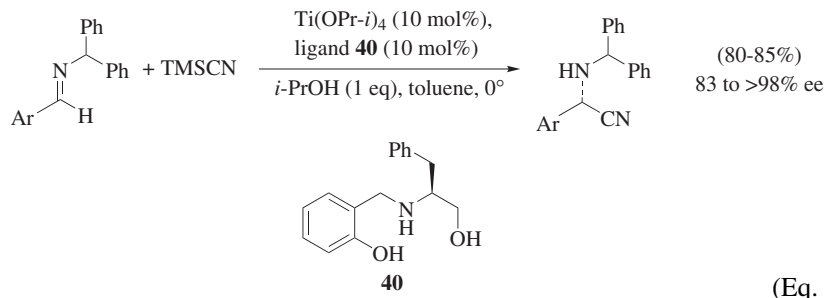
Other metals that are utilized in catalytic enantioselective Strecker reactions of aldimines are the Group 4 metals titanium and zirconium. The complex generated from $\text{Zr}(\text{O}i\text{Bu})_4$, 6,6'-dibromo-1,1'-bi-2-naphthol (**36**) or 3,3'-dibromo-1,1'-bi-2-naphthol (**37**), and *N*-methylimidazole (NMI) is a general asymmetric catalyst that produced high enantioselectivity in the reactions between aldimines and $(n\text{-Bu})_3\text{SnCN}$ (Eq. 19).^{51,75} The structure of the asymmetric catalyst was proposed as **38** based on NMR studies. The free phenolic group of the imine is essential for high enantioselectivity as well as high chemical yield. This reaction was extended to a three-component catalytic enantioselective Strecker reaction. Thus, the Strecker products were obtained with high enantioselectivity from a mixture of aldehydes, *o*-hydroxyaniline derivatives, and HCN in the presence of 1–5 mol% of the chiral Zr catalyst (Eq. 20).^{51,76} The products were converted to amino acid derivatives through methylation of the phenolic OH, conversion of the nitrile to the methyl ester, and oxidative removal of the *N*-protecting group.



Titanium catalysts derived from peptide **39** promoted the enantioselective Strecker reaction of *N*-benzhydryl aldimines and TMSCN (Eq. 21).^{28–30} The catalyst can be systematically tuned, and the optimal catalyst structure is different depending on the substrate. Slow addition of *i*-PrOH to the reaction mixture dramatically accelerated the reaction rate. The protic additive generated the actual nucleophile, HCN, in situ from TMSCN, and also facilitated the catalyst turnover step. The reaction was proposed to proceed through a dual activation mechanism as depicted in model **9**.



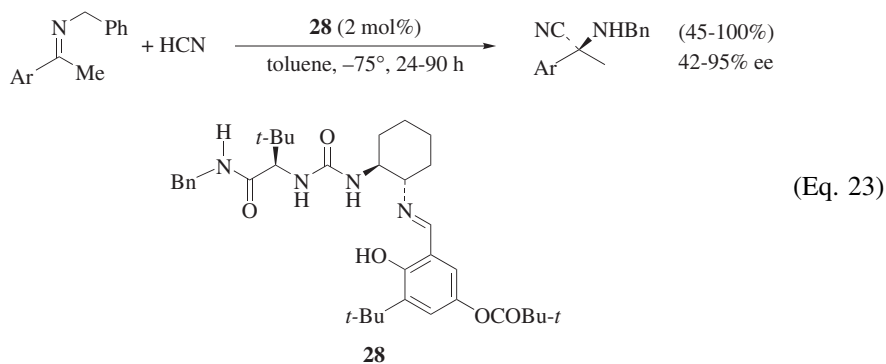
A chiral titanium complex generated from an easily accessible *N*-salicyl- β -aminoalcohol **40** can also promote a highly enantioselective Strecker reaction of aromatic aldimines (Eq. 22).⁷⁷



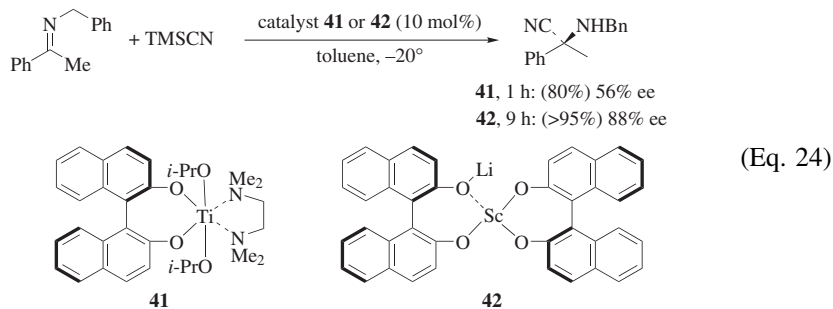
Catalytic Enantioselective Strecker Reaction of Ketimines

α,α -Disubstituted amino acids are important chiral building blocks for biologically active compounds, such as enzyme inhibitors and conformationally restricted peptide mimetics.⁷⁸ The catalytic enantioselective Strecker reaction of ketimines is a very useful reaction for the synthesis of enantiomerically enriched α,α -disubstituted amino acids. Normally, ketimines are much less reactive than aldimines. In addition, differentiation of the two substituents (aryl vs. aryl, aryl vs. alkyl, or alkyl vs. alkyl groups) on the prochiral carbon of ketimines is much more difficult compared to those on aldimines (aryl or alkyl vs. hydrogen). Therefore, asymmetric catalysts that can promote the Strecker reaction of ketimines need to be more active and enantioselective than those promoting reactions of aldimines.

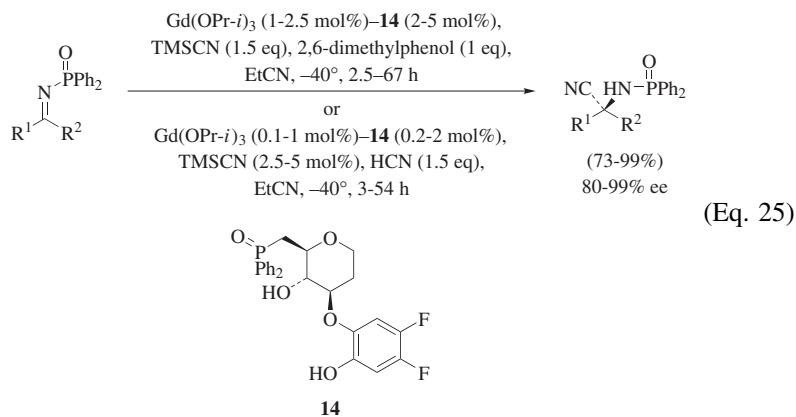
Chiral urea **28** and its solid-supported derivative are efficient catalysts for enantioselective Strecker reactions of aryl methyl ketimines (Eq. 23).³⁸ Aliphatic ketimines and ethyl-substituted ketimines react with moderate (41–69% ee) enantioselectivity.



Chiral titanium catalyst **41** derived from BINOL⁷⁹ and heterobimetallic catalyst **42**⁸⁰ have been shown to promote the asymmetric Strecker reaction of an acetophenone-derived ketimine (Eq. 24). However, this was the only substrate studied in these reactions.



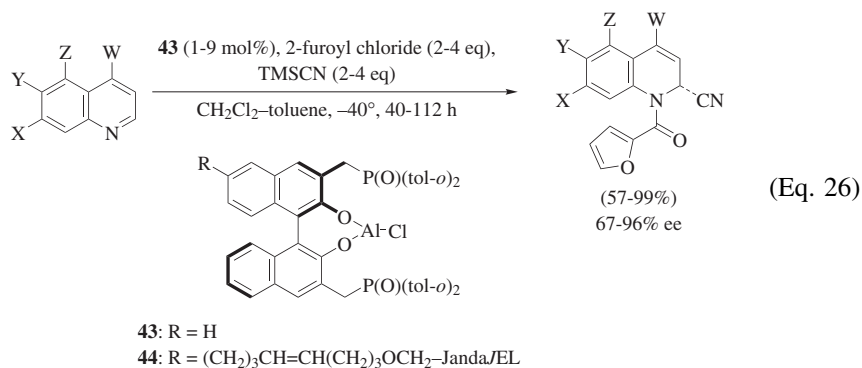
A synthetically useful catalyst for the enantioselective Strecker reaction of ketimines is a gadolinium complex derived from ligand **14** (Scheme 1).^{39–41} This catalyst was prepared from $\text{Gd}(\text{OPr-}i)_3$ and **14** in a 1:2 ratio. Excellent enantioselectivities were obtained from a wide range of *N*-diphenylphosphinoyl ketimines (aromatic, heteroaromatic, and aliphatic) in the presence of minimal catalyst loadings (0.1–2.5 mol%). The reaction can be performed either in the presence of a stoichiometric amount of TMSCN and 2,6-dimethylphenol⁴⁰ or the combination of a catalytic amount of TMSCN and a stoichiometric amount of HCN (Eq. 25).⁴¹ Using the latter combination, excellent catalyst turnover (up to 1000) was observed. The *N*-diphenylphosphinoyl group was easily removed under acidic conditions.



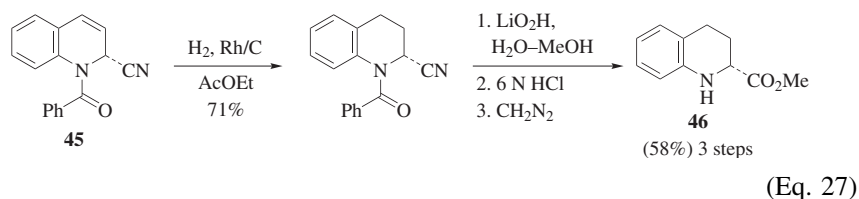
Catalytic Enantioselective Reissert Reaction

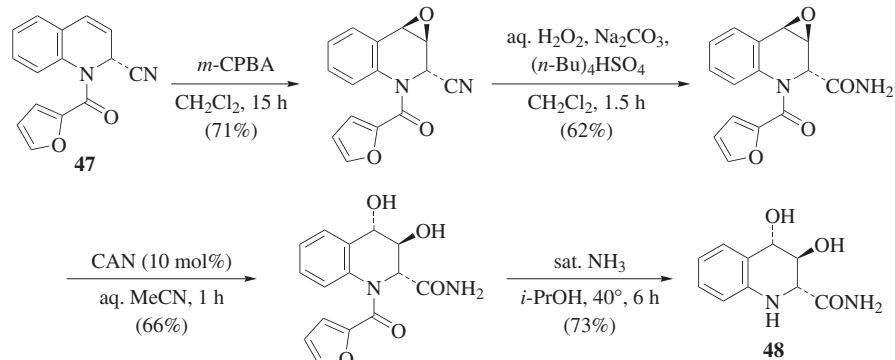
The catalytic enantioselective Reissert reaction is very useful for the synthesis of biologically active compounds containing *N*-heterocycles. The reaction requires the use of strong electrophiles such as acyl chlorides. In addition, TMSCl is generated during the course of the reaction when TMSCN is used as a cyanide source. Therefore, an asymmetric catalyst should be tolerant toward these strong electrophiles. The catalytic enantioselective Reissert reaction of quinolines was developed using BINOL-derived Lewis acid–Lewis base bifunctional catalyst **43** (Eq. 26).^{47,48} The use of 2-furoyl chloride and methylene chloride/toluene mixed

solvent gave the best results with the fewest side-products. In addition, ligand **43** containing di(*o*-tolyl)phosphine oxide as a Lewis base to activate TMSCN produced slightly improved enantioselectivity compared to the original bifunctional catalyst **6** containing diphenylphosphine oxide. Generally, quinolines containing electron-donating substituents resulted in higher yields and enantioselectivities as compared to those containing electron-withdrawing substituents. This tendency is consistent with the following results obtained from mechanistic studies: (1) the rate-determining step of the Reissert reaction is the catalyst-independent acyl quinolinium formation, and (2) the catalyst-independent background cyanation of an acyl quinolinium intermediate is faster for electron-deficient substrates. The reaction was conducted using the Janda/JEL-supported catalyst **44**; the enantioselectivity, however, was slightly lower than with the soluble catalyst **43**. The solid-supported catalyst **44** was recyclable and the aluminum was retained, although the enantioselectivity decreased with each run (from 86% ee in the first run using **44** to 64% ee in the fourth run).



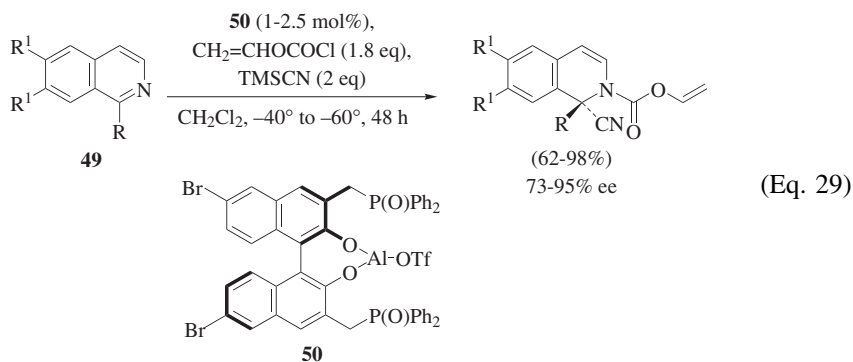
Taking advantage of the multifunctionality of the quinolinium products, several subsequent useful transformations were possible. An enantiomerically enriched tetrahydroquinoline-2-carboxylate derivative **46** was synthesized from the Reissert product **45** via rhodium-catalyzed hydrogenation followed by hydrolysis and methyl esterification, without any loss of enantiopurity (Eq. 27). In addition, epoxidation of cyanoquinoline derivative **47** proceeded selectively from the side opposite to the nitrile (Eq. 28). After conversion of the nitrile to an amide, regioselective epoxide ring-opening with water using ceric ammonium nitrate (CAN) followed by cleavage of the *N*-furoyl amide produced functionalized tetrahydroquinoline **48** containing three contiguous stereocenters.





(Eq. 28)

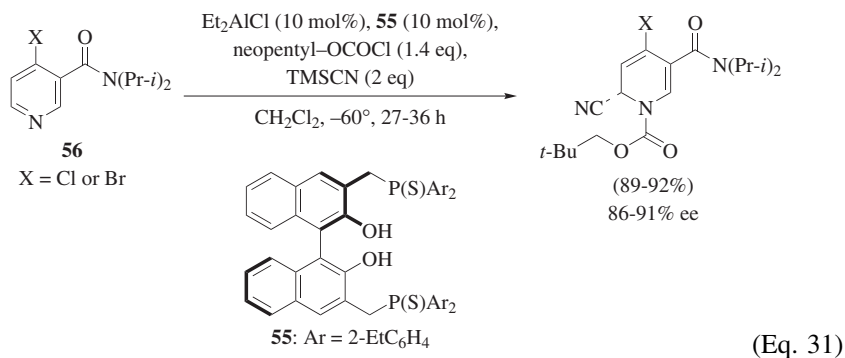
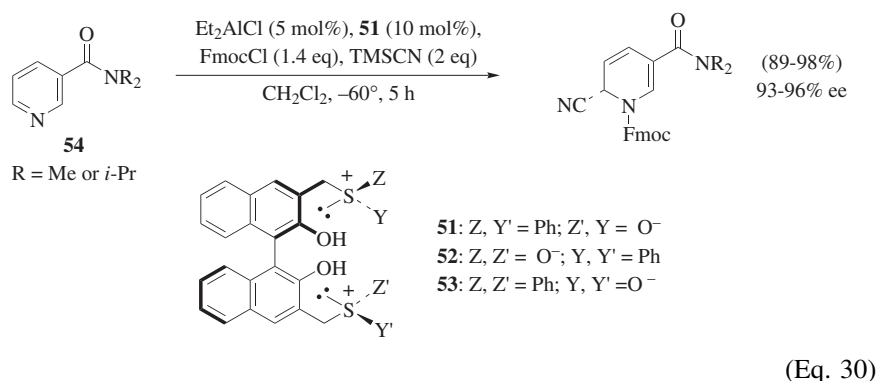
The catalytic enantioselective Reissert reaction was applied to the synthesis of quaternary stereocenters by tuning the bifunctional catalyst (Eq. 29).⁴⁹ To overcome the attenuated reactivity of substrate **49**, catalyst **50** containing an enhanced Lewis acidity was developed. The Lewis acidity of aluminum in complex **50** should be higher than in the previous catalysts **6** or **43** due to the electron-withdrawing bromine substituents on the BINOL core and the electronegativity of the triflate anion. Excellent enantioselectivity was obtained from a number of highly substituted isoquinolines. The reaction was utilized as a key step in the catalytic asymmetric synthesis of several biologically active compounds (see “Applications to Synthesis”).



(Eq. 29)

Chiral piperidines are among the most important building blocks for biologically active compounds. The catalytic enantioselective Reissert reaction of pyridine derivatives can produce such chiral building blocks. An asymmetric catalyst prepared from Et_2AlCl and chiral ligand **51** in a 1 : 2 ratio promotes the enantioselective Reissert reaction of nicotinamide derivatives **54** with excellent regio- and enantioselectivity (Eq. 30).⁵⁰ The electron-withdrawing amide functional group at the 3-position of the substrates is essential for high conversion and enantioselectivity, and the configuration of the sulfoxides at the 3,3'-positions of

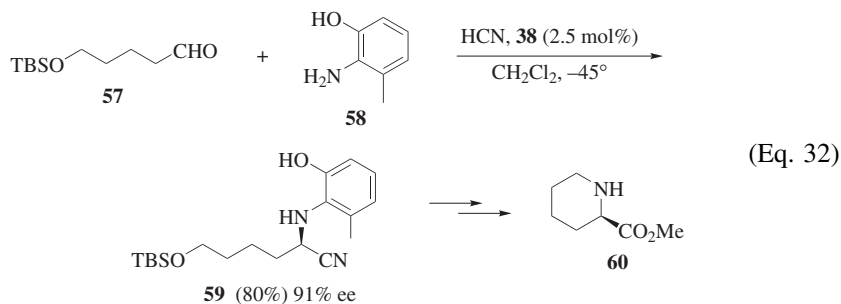
the ligand is also critical for the observed high selectivity. The aluminum complexes derived from the C-2-symmetric ligands **52** and **53** are poor catalysts in terms of catalyst activity, enantioselectivity, and regioselectivity. On the basis of structural studies of the active catalyst using mass spectroscopy, a 2 : 3 complex of aluminum and ligand **51** is proposed to be the active enantioselective catalyst. Proper configurational matching between the axial chirality of the BINOL core and central chiralities of the two sulfoxides is essential for the stabilization of the active bimetallic catalytic species, and thus for the high regio- and enantioselectivity. Ligands **52** and **53** did not generate the corresponding 2 : 3 complexes. A different type of enantioselective bifunctional catalyst, generated from Et₂AlCl and phosphine sulfide-containing ligand **55** in a 1 : 1 ratio, was the optimal catalyst for slightly different substrates **56** containing a halogen substituent at the 4-position of the pyridine core (Eq. 31).⁵⁰



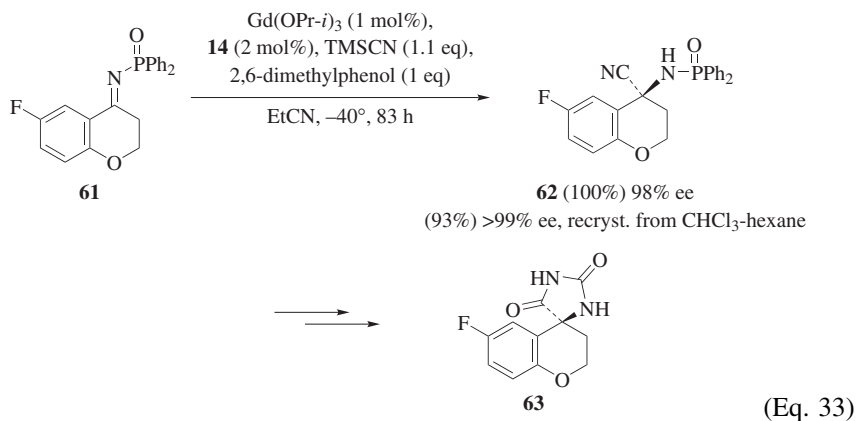
APPLICATIONS TO SYNTHESIS

The importance of catalytic enantioselective Strecker and Reissert reactions is demonstrated by their effective use in the synthesis of biologically active compounds. The catalytic enantioselective three-component Strecker reaction of aldehyde **57**, aniline derivative **58**, and HCN using 2.5 mol% of chiral zirconium catalyst

38 produced the corresponding product **59** in 80% yield with 91% ee. This product was converted to D-pipecolic acid methyl ester (**60**) in three steps (Eq. 32).⁵¹

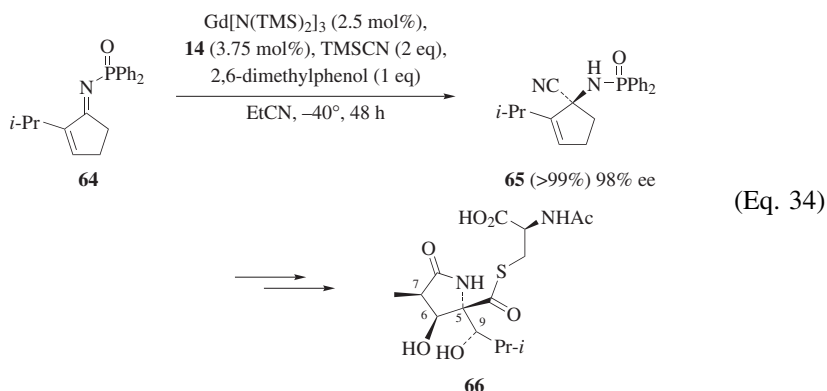


Sorbinil (**63**) is a highly potent aldose reductase inhibitor, considered to be a pharmaceutical lead for the treatment of diabetic neuropathy.⁸¹ Sorbinil contains a spirohydantoin structure with a quaternary stereocenter. A concise catalytic enantioselective synthesis of sorbinil was achieved using the catalytic enantioselective Strecker reaction of ketimine **61** as the initial key step (Eq. 33).⁴⁰ Product **62** was obtained in quantitative yield with 98% ee using 1 mol% of the gadolinium complex derived from ligand **14**. Enantiomerically pure **62** was obtained through one recrystallization. Synthesis of **63** was completed in three steps from intermediate **62**.

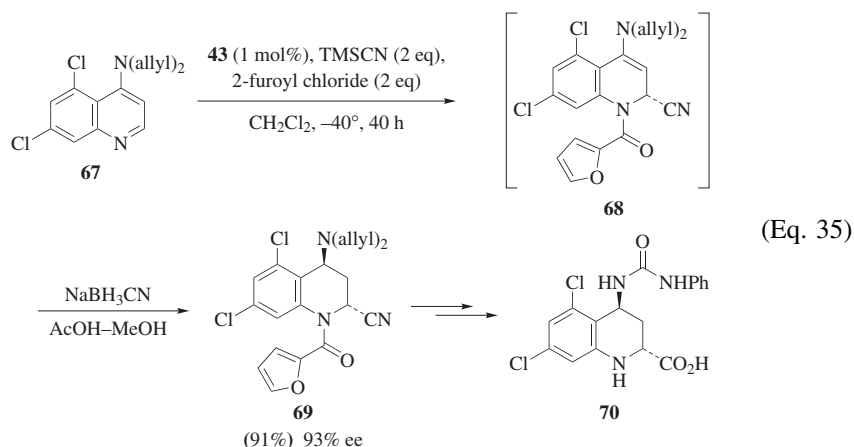


Lactacystin (**66**) is a potent and selective proteasome inhibitor isolated from *Streptomyces* by Omura and coworkers.⁸² It contains a quaternary stereocenter in a highly substituted γ -lactam ring. Due to its challenging structure, many synthetic chemists have studied and achieved the total synthesis of lactacystin.^{83–85} The catalytic enantioselective Strecker reaction using a gadolinium catalyst was applied to construct the quaternary stereocenter (C-5) of lactacystin starting from *N*-phosphinoyl imine **64** (Eq. 34).⁸⁶ The catalyst prepared from $\text{Gd}[\text{N}(\text{TMS})_2]_3$ and ligand **14** in a 1 : 1.5 ratio gave the best results. The reaction was completed

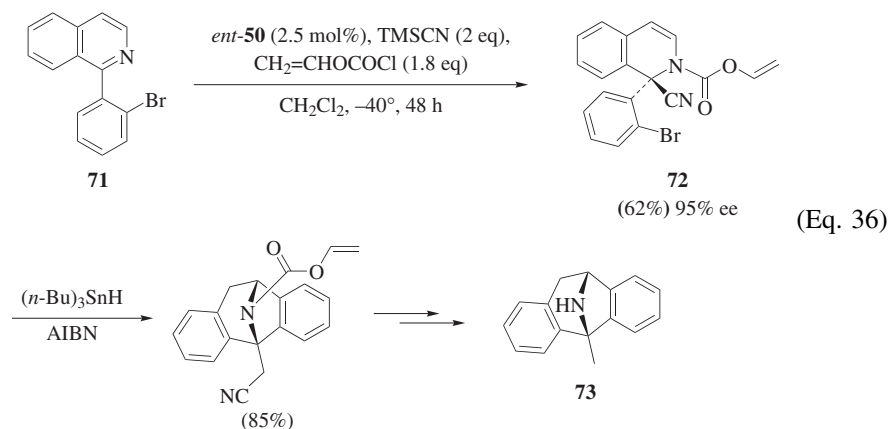
in two days using 2.5 mol% of catalyst, and produced chiral product **65** in quantitative yield and 98% ee. The chiral catalyst prepared from Gd(O-Pr-*i*)₃ and **14** in a 1 : 2 ratio as used in Eq. 33 produced less satisfactory results. Three of the other stereogenic centers (C-6, 7, and 9) of lactacystin, except for the one derived from cysteine, were controlled by the configuration of the quaternary stereocenter at C-5 with excellent stereoselectivity.



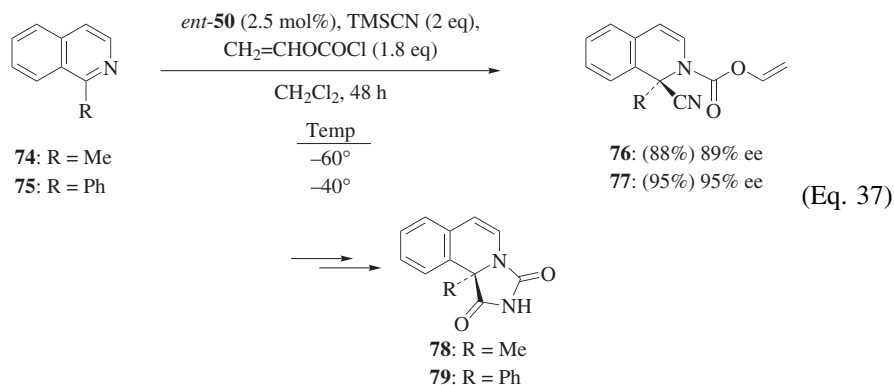
L-689,560 (**70**) is a potent NMDA (*N*-methyl-D-aspartate) receptor antagonist identified by the Merck group.⁸⁷ The synthesis involved the catalytic enantioselective Reissert reaction of quinoline **67** using 1 mol% of aluminum catalyst **43** (Eq. 35).⁴⁸ When the Reissert reaction was complete, intermediate enamine **68** was reduced in situ by subsequent addition of NaBH₃CN, AcOH, and MeOH. This one-pot catalytic enantioselective Reissert reaction–reduction protocol selectively (>20 : 1) produced **69**, with the cyanide trans to the amine, in 91% yield and 93% ee. Subsequent functional group transformations and enantioenrichment by recrystallization furnished **70** in enantiomerically pure form. Solid-supported catalyst **44** was also utilized in the Reissert reaction of **67**; the enantioselectivity was 86% ee using 3 mol% of **44**.



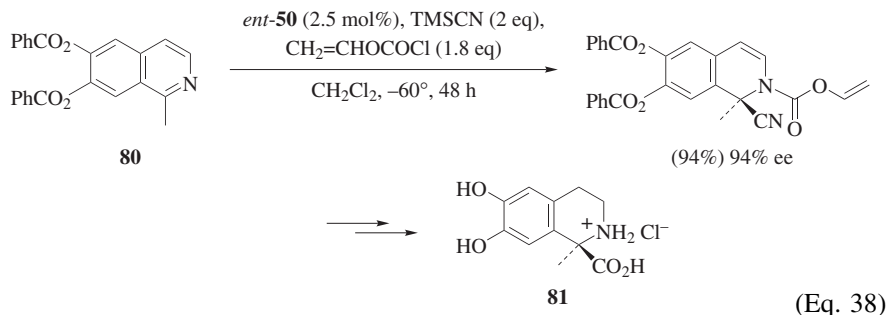
MK801 (dizocilpine, **73**), which contains a quaternary stereocenter,⁸⁸ is another highly potent NMDA receptor antagonist. The synthesis of this agent involved the catalytic enantioselective Reissert reaction of isoquinoline **71** using 2.5 mol% of the enantiomer of catalyst **50** (*ent*-**50**) to form **72** in 62% yield and 95% ee.⁴⁹ Subjecting **72** to radical cyclization conditions using (*n*-Bu)₃SnH and AIBN produced the tetracyclic core. Synthesis of MK801 was completed through a series of functional group transformations (Eq. 36).



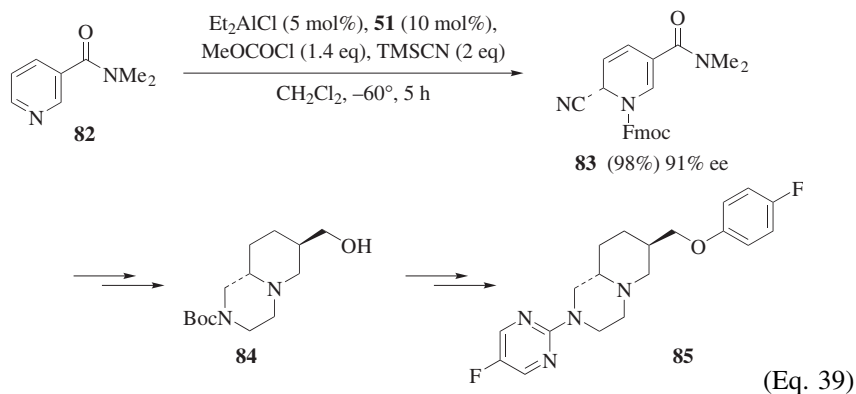
Anticonvulsant phenytoin analogues **78** and **79**⁸⁹ were synthesized using the catalytic enantioselective Reissert reaction of compounds **74** and **75**, respectively (Eq. 37).⁴⁹ Thus, the Reissert reaction of these two substrates in the presence of catalyst *ent*-**50** produced the corresponding products **76** and **77** with high enantioselectivity. These compounds were converted to the target molecules **78** and **79** through hydrogenation and hydrolysis of the nitrile.



The catalytic enantioselective Reissert reaction of isoquinoline **80** was utilized as a key step for the synthesis of biosynthetic intermediate **81**⁹⁰ of a dopamine-derived alkaloid salsolinol (Eq. 38).⁴⁹ The Reissert reaction of **80** proceeded with excellent yield and enantioselectivity using *ent*-**50** as the catalyst.

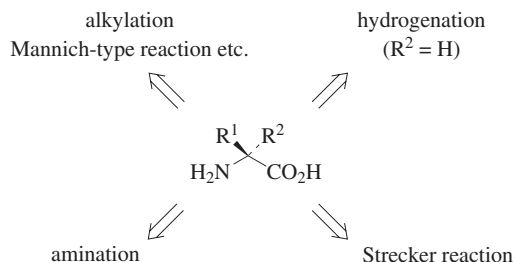


An asymmetric formal synthesis of a dopamine D₄-receptor-selective antagonist CP-293,019 (**85**)⁹¹ was achieved using the catalytic enantioselective Reissert reaction of pyridine derivative **82** as a key step (Eq. 39).⁵⁰ The Reissert reaction of **82** using a catalyst derived from Et₂AlCl and a chiral sulfoxide-containing ligand **51** in a 1:2 ratio produced the corresponding product **83** in 98% yield with 91% ee. The known key intermediate **84** was synthesized from **83** in several steps.



COMPARISON WITH OTHER METHODS

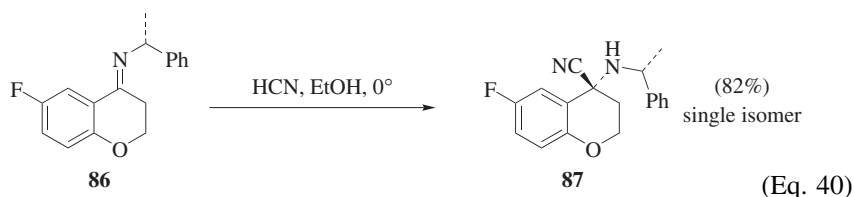
Due to the importance of α -amino acids in a variety of fields, a number of excellent stereoselective methods have been developed for their synthesis.¹⁻⁶ As shown in Scheme 2, there are mainly four types of retrosynthetic bond disconnection. Any non-stereoselective reactions for the synthesis of α -amino acids can theoretically be extended to asymmetric synthesis using the chiral auxiliary method. Asymmetric synthesis of α -amino nitriles through the chiral auxiliary method is the main focus of this section. However, given the importance of and current emphasis on developing catalytic enantioselective reactions, three other types of catalytic enantioselective methods for chiral α -amino acid synthesis are also discussed in some detail.



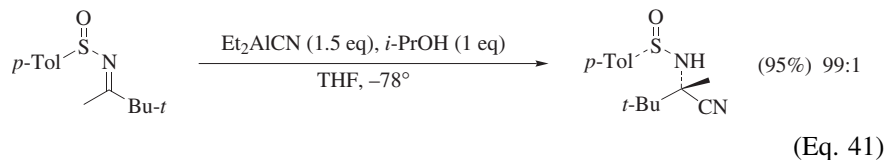
Scheme 2

Chiral Auxiliary-Controlled Asymmetric Strecker Reaction

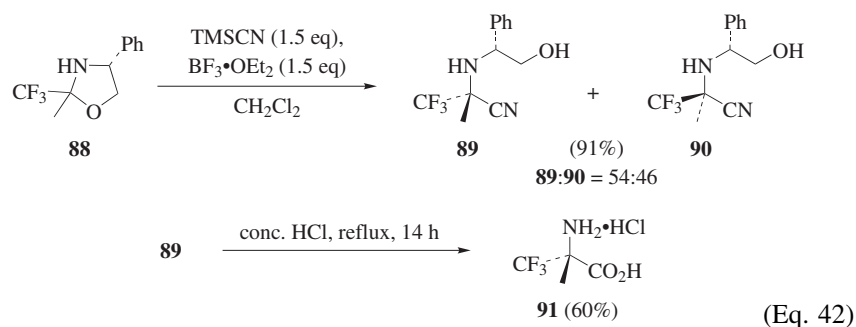
It is possible to control the stereochemistry of the Strecker reaction by introducing a chiral auxiliary to the amine moiety of substrates. There are two main features of this methodology: (1) the diastereoselection is reliable and predictable, and (2) the enantiomeric purity of the target compounds can be easily enriched through separation of the intermediate diastereomers even if the initial stereoselectivity is not completely satisfactory. Disadvantages of the chiral auxiliary method are that a stoichiometric amount of a chiral source is always required, and that chiral auxiliaries normally decompose during the deprotection of the nitrogen atom to obtain final target amino acids. Therefore, the use of inexpensive chiral auxiliaries is essential. Imines derived from 1-phenylethylamine (or its analogues)^{81,92–105} and chiral *N*-sulfinyl imines^{106–111} are two representative chiral substrates used in the asymmetric Strecker reaction. The diastereoselectivity of 1-phenylethylamine-derived imines is normally moderate (ca. 1.5 : 1 to 4 : 1),^{93,94,95,100} with some exceptions. When high diastereoselectivity was obtained (Eq. 40), reversible cyanide addition occurred concomitantly with fractional crystallization.⁸¹ The desired diastereomer **87** was obtained from **86** as a single isomer in 82% yield. The product is a key synthetic intermediate of an aldose reductase inhibitor.



Chiral *N*-sulfinyl ketimines afford high diastereoselectivity in the Strecker reaction (Eq. 41).¹⁰⁸ The chiral auxiliary is removed under acidic conditions, and α,α -disubstituted amino acid derivatives are obtained with high enantiomeric purity.

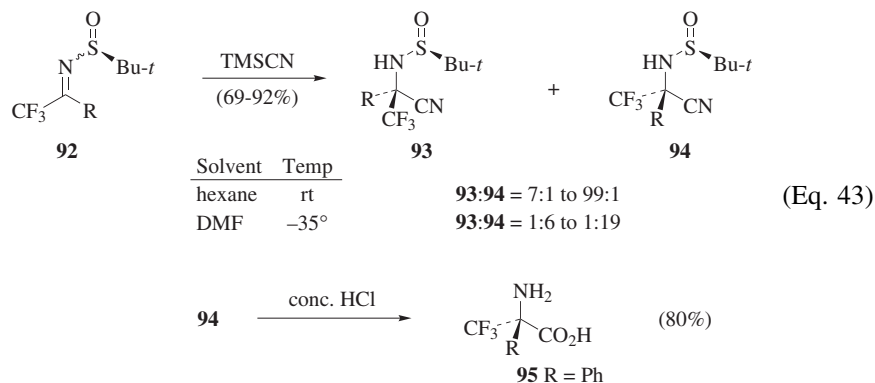


To highlight the utility of the chiral auxiliary-controlled method, two recent examples of the asymmetric Strecker reaction of trifluoromethyl ketone-derived imines are described. A diastereoselective Strecker reaction of chiral oxazolidine **88** containing a phenylglycinol auxiliary proceeded with moderate to low selectivity in the presence of 1.5 eq of $\text{BF}_3 \cdot \text{OEt}_2$ (Eq. 42).¹¹² The resulting diastereomers **89** and **90** were separable by silica gel column chromatography. The diastereomerically pure **89** was converted to trifluoromethylalanine hydrochloride (**91**) through acid hydrolysis in 60% yield.



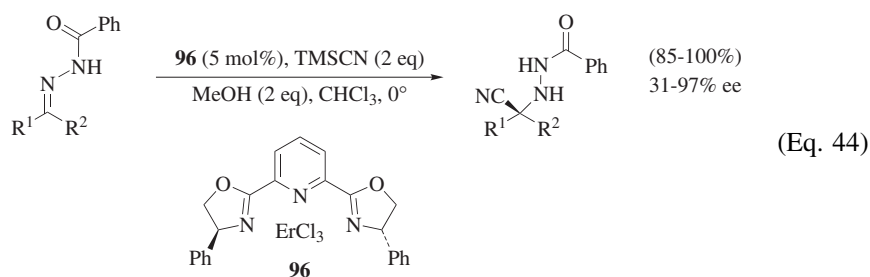
Highly diastereoselective Strecker reactions of trifluoromethyl-substituted *N*-sulfinyl imine **92** have been reported (Eq. 43).¹¹³ Imine **92** can be synthesized through condensation between trifluoromethylketones and the corresponding enantiomerically pure sulfonamide in the presence of an excess amount (1.5 eq) of $\text{Ti}(\text{OPr-}i)_4$.^{114,115} Trifluoromethyl-substituted sulfinyl amides **92** are not very stable, and should be generated and purified quickly prior to use. The diastereoselectivity of this Strecker reaction was strongly dependent on the solvent. When non-coordinating hexane was used as a solvent, isomer **93** was obtained as the major diastereomer. However, the other isomer **94** was the major product when highly coordinating DMF was used as a solvent. The authors attributed this dramatic solvent effect to the switch of the transition state from cyclic (in hexane) to acyclic (in DMF). In hexane, the oxygen atom of the sulfinyl amide acts as a Lewis base to activate TMSCN. On the other hand, the oxygen atom of DMF activates TMSCN, thus liberating the oxygen atom of the sulfinyl amide from coordination to silicon. Isolated diastereomer **94** was converted to amino acid **95** via acid hydrolysis. Currently, there is no

catalytic enantioselective Strecker reaction that is effective with trifluoromethyl-substituted aldimines and ketimines. Therefore, the diastereoselective methods are the only asymmetric approaches to access chiral trifluoromethyl-substituted amino acids.



Catalytic Asymmetric Hydrocyanation of Hydrazones

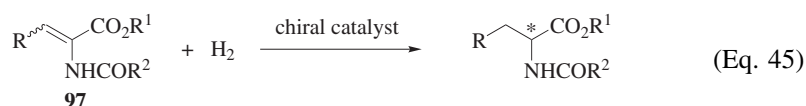
Hydrazones can be considered to be stable surrogates for imines. Despite the existence of several examples of racemic cyanation of hydrazones,^{116,117} including a Lewis acid catalyzed reaction,¹¹⁸ there is only one catalytic enantioselective variant reported (Eq. 44).¹¹⁹ An ErCl_3 -PhPyBox (**96**) complex was used as an asymmetric catalyst (5 mol%). Hydrazones derived from aromatic aldehydes afforded high enantioselectivity (76–97% ee). Aliphatic substrates and ketone-derived hydrazones, however, produced only moderate enantioselectivity.



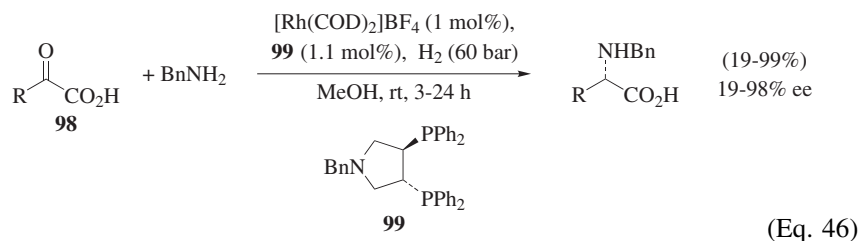
Catalytic Asymmetric Hydrogenation

Asymmetric hydrogenation of dehydroamino acids **97** by chiral rhodium or ruthenium catalysts is one of the most general and reliable methods for the synthesis of α -amino acid derivatives (Eq. 45). Because this reaction is fundamental

and has been extensively reviewed,^{120–128} it will not be discussed here in detail. Excellent catalyst turnover rates, catalyst turnover numbers, and enantioselectivities are generally obtained. This method is used practically for large-scale syntheses of chiral α -amino acids. α,α -Disubstituted amino acids, however, cannot be synthesized using this method.

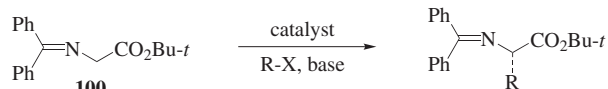


A potentially important but much less studied catalytic asymmetric hydrogenation route to chiral α -amino acids is the reductive amination of α -keto acids **98**. A catalytic enantioselective hydrogenative amination of **98** in the presence of *N*-benzylamine and 1 mol% of a chiral rhodium complex derived from **99** proceeded with moderate to excellent enantioselectivity (Eq. 46).¹²⁹ The reaction conditions were tolerant of the carboxylic acid functional group.

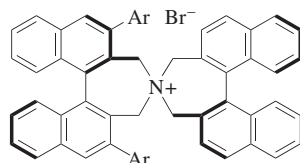
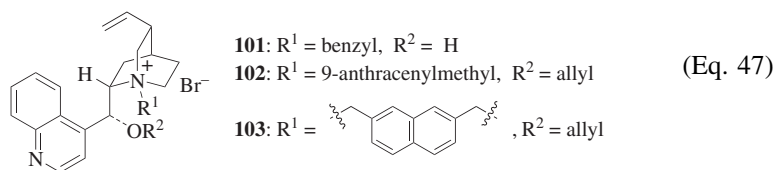


Catalytic Asymmetric Introduction of the Side Chain through C–C Bond Formation

Asymmetric Phase-Transfer-Catalyzed Reactions. The asymmetric alkylation of glycine-derived Schiff base ester **100** using chiral phase-transfer catalysis is an alternative approach to chiral α -amino acids.^{5,130,131} Phase-transfer catalysis generally offers the following advantages: (1) mild reaction conditions, (2) simple reaction procedures, and (3) the use of safe and inexpensive reagents and solvents. Thus, the reaction can be easily conducted both on small and large scales. Chiral phenylglycine derivatives, however, cannot be synthesized using the phase-transfer methodology. Since the first report of catalytic enantioselective alkylation of **100** using cinchona alkaloid-derived phase-transfer catalyst **101**,¹³² the efficiency has been significantly improved by modifying the catalyst structure (Eq. 47). Specifically, *N*-9-anthracenylmethyl catalyst **102**^{133,134} and a catalyst containing two cinchona alkaloid moieties (**103**)¹³⁵ are highly effective asymmetric catalysts.



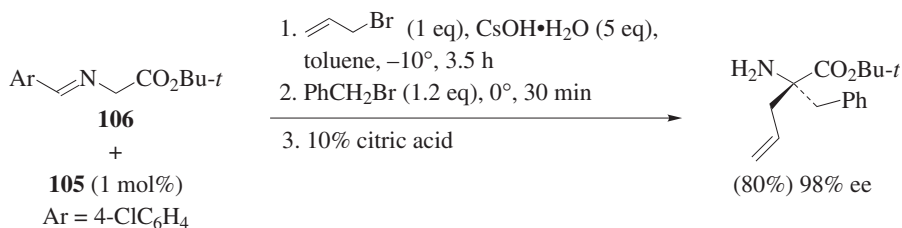
Catalyst	mol%	Solvent	R = Bn			
			Temp	Time	Yield	% ee
101	10	CH ₂ Cl ₂	rt	9 h	(75%)	64
102	10	CH ₂ Cl ₂	-78°	23 h	(87%)	94
103	1	toluene-CH ₂ Cl ₂	0°	10 h	(95%)	97
104	0.2	toluene	0°	12 h	(81%)	98



104: Ar = 3,5-Ph₂C₆H₃

105: Ar = 3,4,5-F₃C₆H₂

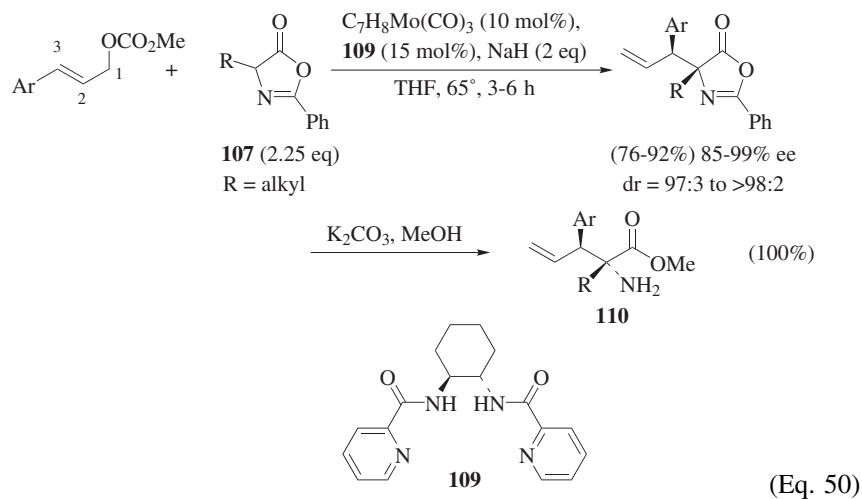
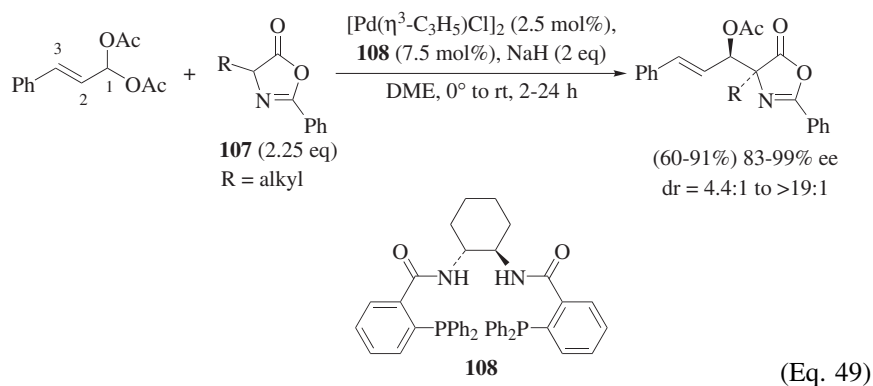
The most useful asymmetric phase-transfer catalysts in terms of enantioselectivity, substrate generality, and catalyst activity are the binaphthyl-derived quaternary ammonium salts **104** and **105**.^{136,137} It is noteworthy that the method can be applied to a catalytic asymmetric synthesis of α,α -dialkyl-substituted amino acids using sterically less crowded prenucleophile **106** (Eq. 48). The absolute configuration of the quaternary stereocenter can be controlled by the order of addition of the alkylating reagents.



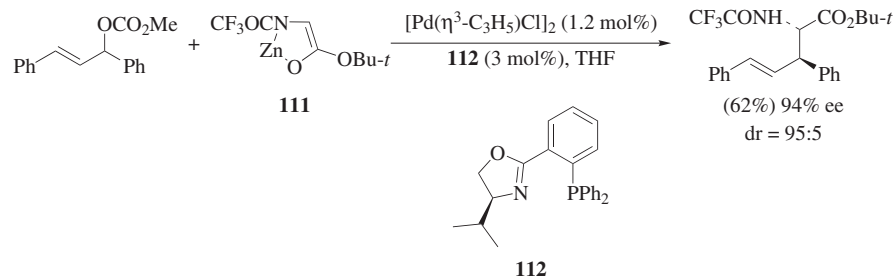
(Eq. 48)

Asymmetric Allylic Substitution Catalyzed by Chiral Transition Metal Complexes. The catalytic asymmetric allylic substitution by azlactone **107**

produces enantiomerically enriched precursors of α,α -disubstituted amino acids. Two kinds of constitutional isomers can be formed selectively, depending on the asymmetric catalyst used (Eqs. 49 and 50). Using the palladium catalyst containing chiral diphosphine ligand **108**, substitution occurs at the C-1 position having the acetoxy leaving group.^{138,139} Using a molybdenum catalyst derived from ligand **109**, the substitution occurs at C-3.¹⁴⁰ High enantio- and diastereo selectivities are obtained in both reactions. The product azlactone was solvolyzed in basic methanol to give the amino acid derivative **110** in quantitative yield.

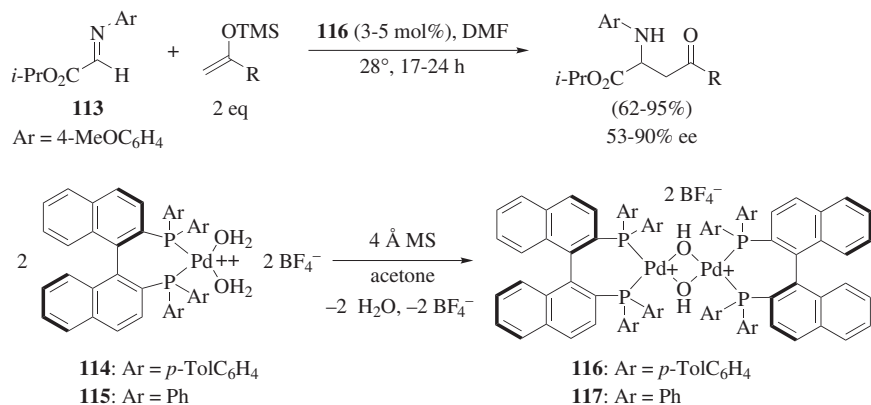


An asymmetric allylic substitution by zinc enolates (such as **111**) derived from N-protected glycine esters catalyzed by a chiral palladium complex and ligand **112** has been reported (Eq. 51). The substrate generality of this reaction is not very broad.¹⁴¹

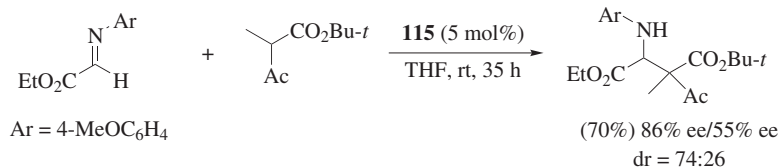


(Eq. 51)

Catalytic Asymmetric Addition to Imino Esters. Imino esters (**113**, **118**, or **121**) are reactive electrophiles, and they have been used in various catalytic asymmetric carbon–carbon bond-forming reactions (e.g. the Mannich-type reactions) using diverse nucleophiles. Enol silyl ethers react with **113** in the presence of the chiral cationic palladium catalyst **116** with high enantioselectivity (Eq. 52).¹⁴² The binuclear μ -hydroxo complex **116** was prepared from the mononuclear dicationic palladium complex **114** through treatment with 4 Å molecular sieves in acetone. The dicationic complex **114** did not induce any enantioselectivity in the Mannich-type reaction shown in Eq. 52. This reaction was recently extended to the direct addition of β -ketoesters to imino esters using dicationic **115** as an asymmetric catalyst (Eq. 53).¹⁴³ Interestingly, binuclear complex **117** was an unsatisfactory catalyst for this reaction. A three-component reaction involving a glyoxalate, an amine, and a β -ketoester was also reported in which the enantioselectivity was high, but the diastereoselectivity was moderate. Similarly, addition of nitroalkanes was developed with high diastereo- and enantioselectivity from imino ester **113** using cationic copper (II)–chiral bisoxazoline complexes.^{144,145}

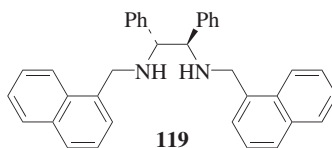
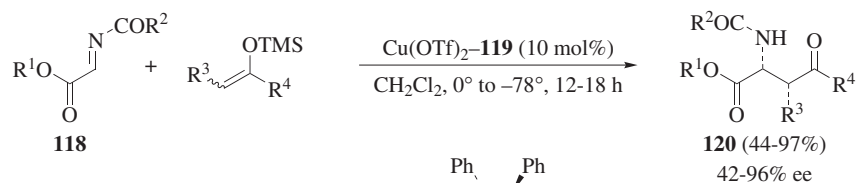


(Eq. 52)



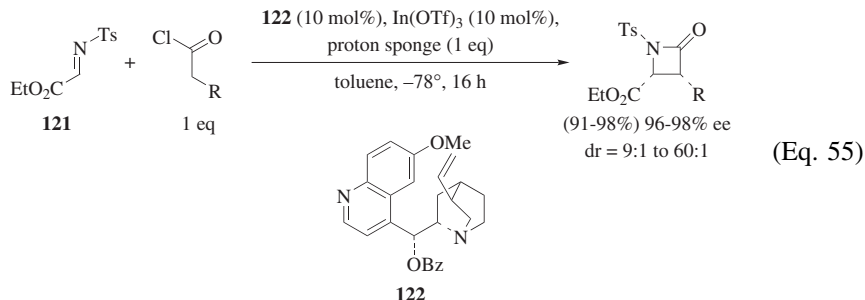
(Eq. 53)

N-Acyl imino esters **118** can be synthesized through elimination of HBr from the corresponding 2-bromoglycine derivative using a polymer-supported amine. The chiral copper(II) triflate–diamine complex **119** catalyzed the asymmetric addition of enol silyl ethers (Eq. 54),^{146,147} alkyl vinyl ethers,¹⁴⁵ and acyl enamides¹⁴⁸ to **118**. Reactions using propionate-derived enol silyl ethers also proceeded with high enantio- and diastereoselectivity. Syn-isomer **120** was produced from both *E*- and *Z*-enolates. The catalytic asymmetric Mannich-type reactions¹⁴⁹ and allylation reactions¹⁵⁰ proceeded in aqueous media (H₂O/THF = 1 : 9) using more stable *N*-acylhydrazone esters as substrates. A combination of zinc fluoride (50 mol%), chiral diamine (related to **119**), and triflic acid (1 mol%) was used as the catalyst. The hydrazine moiety of the products was converted to the amine by reduction with samarium diiodide.

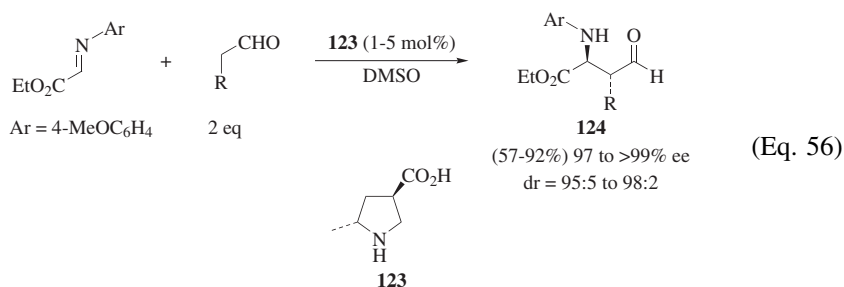


(Eq. 54)

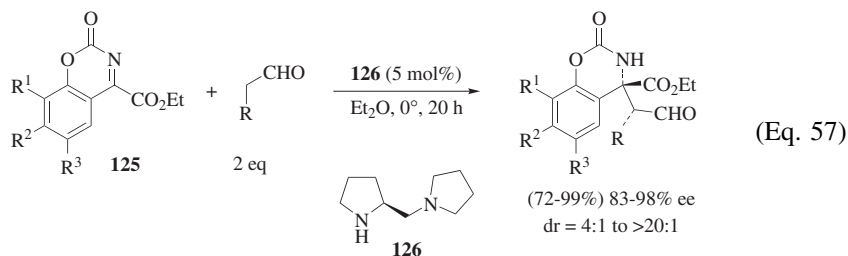
N-Tosylimino esters **121** should be more electrophilic than *N*-acylimino esters, considering the strong electron-withdrawing ability of the tosyl group. The chiral cationic copper(I) complex derived from Tol-BINAP and copper(I) perchlorate is a useful asymmetric catalyst for Mannich-type reactions using enol silyl ethers, ene reactions using alkenes, and allylation reactions using allylsilanes and substrate **121**.¹⁵¹ More recently, a catalytic asymmetric Staudinger-type β -lactam formation (Eq. 55) was reported.¹⁵² A ketene generated in situ from an acid chloride and proton sponge was nucleophilically activated by benzoylquinine (**122**). Addition of 10 mol% of indium triflate, acting as a Lewis acid to activate imine **121**, dramatically accelerated the reaction without affecting the excellent diastereo- and enantioselectivity.



Organocatalysts can promote direct asymmetric Mannich-type reactions of ketones or aldehydes to imino esters.^{153–163} Generally, proline-catalyzed or dinuclear zinc-catalyzed¹⁶⁴ direct asymmetric Mannich-type reactions between imino esters and α -substituted ketones or aldehydes result in syn products with excellent diastereo- and enantioselectivity. Through logical consideration of the transition state structure, an anti-selective direct asymmetric Mannich-type reaction between imino esters and aldehydes producing **124** was developed using 3-pyrrolidinecarboxylic acid derivative **123** as a catalyst (Eq. 56).¹⁶⁵

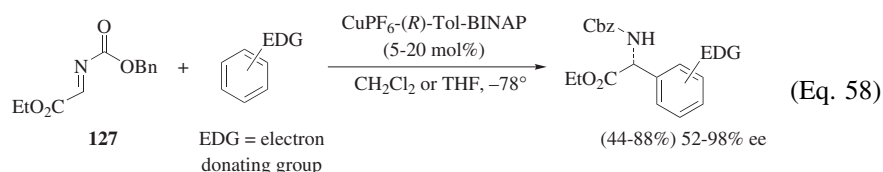


The organocatalyzed direct asymmetric Mannich-type reaction was extended to the synthesis of quaternary stereocenters using a special keto imino ester **125** as a substrate (Eq. 57).¹⁶⁶ The proline-derived diamine **126** produced high diastereo- and enantioselectivity in the reactions between **125** and aldehydes.

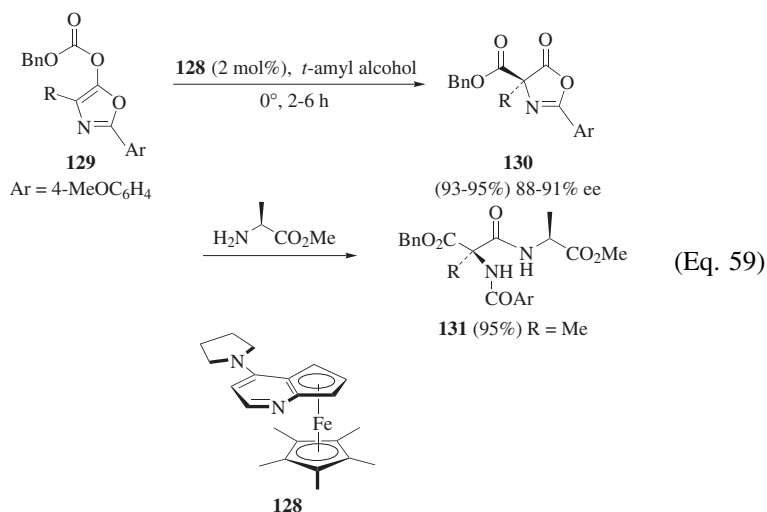


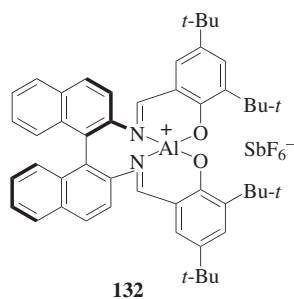
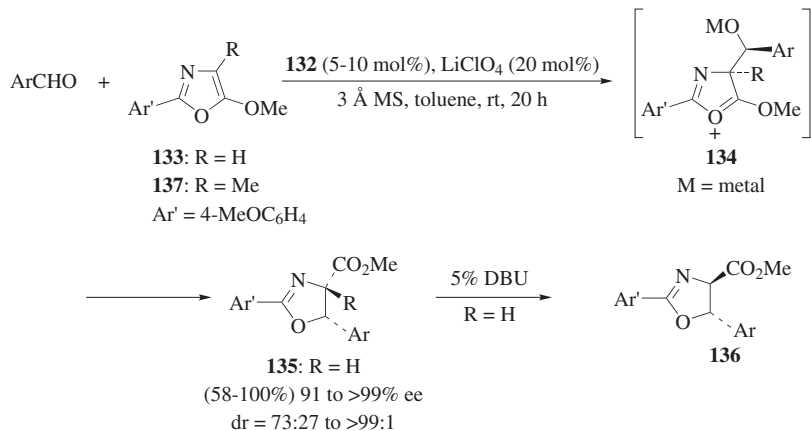
The catalytic enantioselective nucleophilic alkylation of imino esters is much less studied than Mannich-type reactions. *N*-Benzyloxycarbonyl (Cbz) imino esters

127 can react with electron-rich aromatic compounds through a Friedel-Crafts type alkylation under the catalysis of a cationic copper(I)-chiral phosphine complex (Eq. 58).^{167,168} This reaction directly generates enantiomerically enriched *N*-Cbz-protected α -aryl amino esters, which are common intermediates for peptide synthesis. Catalytic enantioselective addition of dialkylzinc to imino esters has been recently reported.¹⁶⁹ The enantioselectivity, however, was in the moderate range.



Oxazole as a Glycine Enolate Equivalent. Oxazole derivatives can be utilized as a glycine enolate equivalent.^{170,171} Two catalytic enantioselective variants have been reported. First, the chiral nucleophilic pyridine derivative **128** catalyzed the enantioselective rearrangement of *O*-acylated azlactone **129** to α,α -disubstituted amino acid derivatives **130** with excellent enantioselectivity and broad substrate generality (Eq. 59).¹⁷² The products were directly converted to protected dipeptides (e.g., **131**) in high chemical yield. Second, chiral aluminum catalyst **132** promoted the addition of **133** to aromatic aldehydes in the presence of a catalytic amount of lithium perchlorate, and the subsequent one-pot rearrangement of **134** afforded *cis*- β -hydroxy- α -amino acid derivatives **135** with excellent diastereo- and enantioselectivity (Eq. 60).¹⁷³ When R=H, the products were isomerized to *trans*-**136** by treatment with 5% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), allowing for the synthesis of both *syn*- and *anti*- β -hydroxy- α -amino acid derivatives. In addition, application to α,α -disubstituted amino acid synthesis was possible using a dicationic copper-bisoxazoline complex as a catalyst and methyl-substituted **137** as a nucleophile.

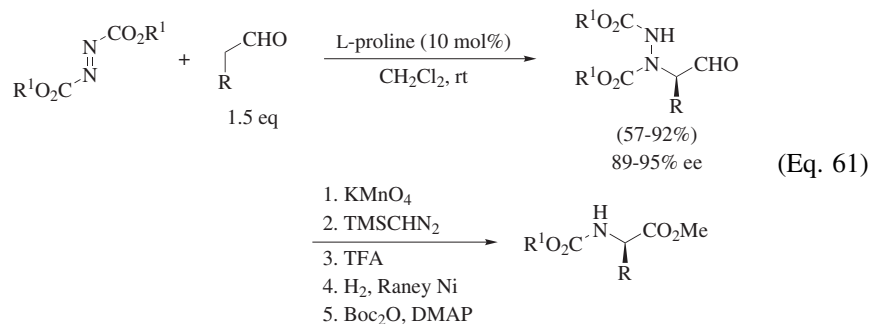




(Eq. 60)

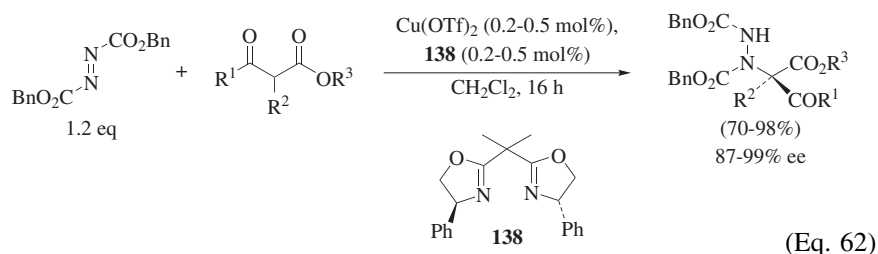
Catalytic Asymmetric Electrophilic Amination of Enolates

Azodiacarboxylates are excellent nitrogen electrophiles in catalytic asymmetric amination of enolate derivatives. Direct organocatalytic asymmetric α -amination of aldehydes has been reported (Eq. 61).¹⁷⁴⁻¹⁷⁶ Excellent enantioselectivity is achieved from a wide range of aldehydes using L-proline as catalysts. The products are converted to amino acid derivatives by oxidation of the aldehyde and reduction of the hydrazine using Raney nickel. The proline-catalyzed asymmetric amination of aldehydes was applied to the syntheses of biologically active pharmaceutical leads.^{177,178}



(Eq. 61)

Chiral cationic copper(II)–bisoxazoline complex **138** catalyzes a general and highly enantioselective α -amination of α -substituted β -ketoesters (Eq. 62).^{179–181} Enantiomerically enriched α,α -disubstituted amino acid derivatives can be synthesized using this reaction. An asymmetric organocatalyzed synthesis of quaternary stereocenters is also possible using α -cyanoacetates as nucleophilic substrates.^{182,183}



EXPERIMENTAL CONDITIONS

Toxicity of Cyanide Compounds

Cyanide compounds (TMSCN, HCN, and KCN) used in the Strecker reaction are highly toxic, and should be handled very carefully in a well-ventilated hood.¹⁸⁴ The toxicity of cyanide is attributed to its extremely high affinity to the iron(III) ion of the mitochondrial cytochrome oxidase enzyme (50% inhibitory concentration = 10^{-8} M). Through the inhibition of this enzyme, the reduced form of cytochrome c, a key electron transporting membrane protein, cannot be converted to the oxidized form, and the respiratory system of cells is blocked. The fatal concentration of HCN for humans after 10 minutes of exposure is 0.2 mg/L, and concentrations over 0.3 mg/L cause instantaneous death.

To prevent any exposure to cyanide, use of appropriate personal protective equipment (gloves, eye glasses, respirator, and HCN gas detector) is indispensable. All solutions containing cyanide should be kept and treated under basic pH. The cyanide waste should be discarded by a special facility, or after oxidative treatment with sodium hypochlorite solution (available chlorine >5%) overnight. If the latter method is used, the remaining cyanide concentration in the treated waste solution should be confirmed by commercial CN^- test paper to be below the detection limit before that solution is discarded.

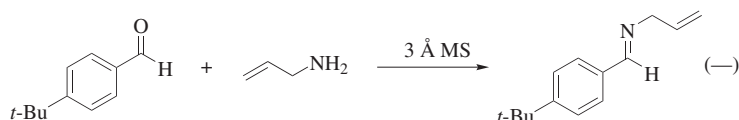
Isolation of Amino Acids

Due to their high polarity, free amino acids synthesized after acid hydrolysis of the Strecker products are generally difficult to isolate and purify using silica gel column chromatography. Taking advantage of the ionic feature of amino acids, however, they can be isolated relatively easily using ion-exchange column chromatography.⁴⁰ The crude mixture after acid hydrolysis of the Strecker products usually contains the target amino acid, a residue derived from the nitrogen protecting group, and ammonium chloride. This mixture is loaded onto an acidic

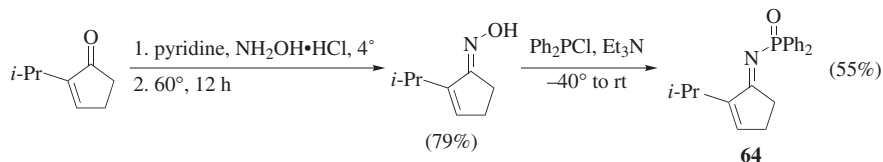
resin (such as acidic Dowex), and the non-charged organic byproduct derived from the nitrogen protecting group is first eluted using methanol. Next, the target amino acid is eluted from the column as the corresponding ammonium salt by changing the eluent to aqueous ammonia. During evaporation of the eluent, the ammonia that is generated through equilibration of the weak acid (carboxylic acid) with the weak base (ammonia) salt is eliminated. Thus, the free amino acid can be obtained.

EXPERIMENTAL PROCEDURES

Preparation of the catalysts referred to in the preceding text and in the experimental procedures may be found by consulting information within references cited.

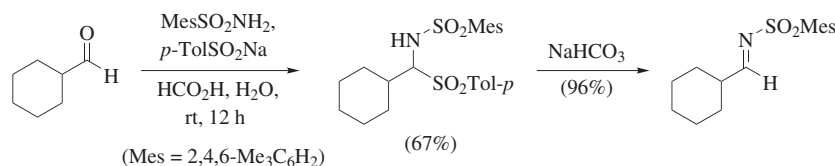


Allyl-(4-*tert*-butyl benzylidene)amine [General Procedure for Preparation of Simple Amine-Derived Aldimines].³³ To a flame-dried 50-mL round-bottom flask, were added activated 3 Å molecular sieves (2 g) and CH₂Cl₂ (20 mL, freshly distilled from CaH₂). To this solution, the substrate benzaldehyde (20 mmol) was added followed by a syringe addition of allylamine (1.3 eq, 26 mmol). After 4 hours, the sieves were removed by filtration and washed with CH₂Cl₂ (2 × 10 mL). The filtrate was collected and the solvent was removed in vacuo. Further purification was accomplished by vacuum distillation to yield the target aldimine. IR (thin film) 2955, 1650, 1462, 1372 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.71 (d, *J* = 10.4 Hz, 2H), 7.45 (d, *J* = 10.4 Hz, 2H), (s, 1H), 6.06 (ddd, *J* = 5.6, 10.3, 17.1 Hz, 1H), 5.24 (dappq, *J* = 1.5, 17.1 Hz, 1H), 5.16 (dappq, *J* = 1.5, 10.3 Hz, 1H), 4.26 (dappq, *J* = 1.5, 5.6 Hz, 2H), 1.35 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 161.7, 153.9, 135.9, 133.4, 127.9, 125.4, 115.6, 63.4, 34.7, 31.1; HRMS (*m/z*): [M⁺] calcd for C₁₄H₁₉N, 201.1517; found, 201.1528.



***N*-(2-Isopropylcyclopent-2-en-1-ylidene)-*P,P*-diphenylphosphinic Amide [General Procedure for Preparation of *N*-Phosphinoyl Ketimines].**^{39,52,86} Pyridine (20.8 mL, 0.26 mol) and hydroxylamine hydrochloride (16.8 g, 0.24 mol) were added to the starting ketone (20 g, 0.16 mol) in EtOH (268 mL)

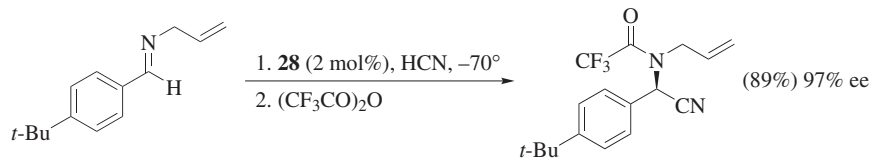
at 4°. After stirring for 15 minutes at 4°, the reaction mixture was warmed to 60° and stirred for 12 hours. Concentration and purification by flash column chromatography (EtOAc/hexane = 1 : 10 to 1 : 5) afforded the corresponding oxime (17.7 g, 79%) as a white solid. To a solution of Et₃N (18.4 mL, 0.13 mol) and the oxime (16 g, 0.12 mol) in CH₂Cl₂ (96 mL) and hexane (96 mL), chlorodiphenylphosphine (27.1 g, 0.13 mol) in CH₂Cl₂ (38 mL) was added slowly over 1 hour at -40°. The reaction mixture was warmed gradually to room temperature, CH₂Cl₂ (100 mL) was added, and the insoluble salt was removed by filtration through a celite pad. The filtrate was concentrated in vacuo. The solid residue was purified by flash column chromatography (CH₂Cl₂/MeOH = 50 : 1 to 20 : 1; EtOAc/MeOH = 20 : 1) to afford the target ketimine (37.4 g) as a white solid. Toluene (75 mL) was added to **64** (37.4 g) and the solution was warmed to 70°, at which point hexane (75 mL) was added. The solution was gradually cooled to room temperature, and the resulting precipitate was collected by filtration to afford pure title compound (25.7 g, total yield 55%) as a white solid, mp 133–134°; IR (neat) = 2959, 1634, 1609, 1192 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.89–7.94 (m, 4H), 7.36–7.43 (m, 6H), 6.99–7.00 (m, 1H), 2.95–2.97 (m, 2H), 2.86 (sept, *J* = 7.0 Hz, 1H), 2.50–2.51 (m, 2H), 1.16 (d, *J* = 7.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 194.2 (d, *J* = 4.9 Hz), 154.2, 154.1, 152.1, 135.7, 134.7, 131.5, 131.5, 131.4, 131.4, 131.1, 131.1, 128.3, 128.3, 128.2, 128.2, 34.3 (d, *J* = 4.9 Hz), 29.4, 25.3, 21.5; ³¹P NMR (CDCl₃) δ 20.7; LRMS–FAB (*m/z*): 324 [M + H]⁺; HRMS–FAB (*m/z*): [M + H]⁺ calcd for C₂₀H₂₃NOP⁺, 324.1512; found, 324.1524.



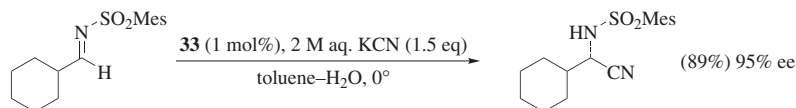
Cyclohexanecarboxaldehyde *N*-(Mesitylenesulfonyl)imine [General Procedure for Preparation of *N*-Sulfonyl Imines].^{58,68} A mixture of cyclohexanecarboxaldehyde (363 μL, 3.0 mmol), mesitylenesulfonamide (598 mg, 3.0 mmol) and sodium *p*-toluenesulfonate (481 mg, 3.0 mmol) in HCO₂H (4.5 mL) and H₂O (4.5 mL) was stirred for 12 hours at room temperature. The resulting white precipitate was filtered off, and washed with H₂O and hexane. The precipitate was then recrystallized from EtOAc/hexane to obtain the intermediate *N*-(mesitylenesulfonyl)- α -(*p*-toluenesulfonyl)cyclohexylmethylamine (301 mg, 2.01 mmol, 67%) as a crystalline material; IR (thin film) 3401, 3285, 3028, 2928, 2855, 1599, 1566, 1450, 1331, 1302, 1155, 1123, 1082, 903, 853, 814, 733 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.81 (s, 2H), 5.27 (d, *J* = 10.7 Hz, 1H), 4.53 (dd, *J* = 3.0, 10.7 Hz, 1H), 2.50–2.40 (m, 1H), 2.42 (s, 6H), 2.34 (s, 3H), 2.29 (s, 3H), 2.11 (d, *J* = 12.3 Hz, 1H), 1.81–1.60 (m, 4H), 1.38–1.28 (m, 2H), 1.19–1.02

(m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.4, 141.7, 137.5, 135.7, 134.2, 131.6, 129.3, 128.3, 77.5, 37.5, 30.7, 27.2, 26.2, 25.8, 25.7, 22.9, 21.7, 21.0.

The sulfonamide sulfone obtained above (901 mg, 2.01 mmol) was dissolved in CH_2Cl_2 (2 mL). Then, saturated aqueous sodium bicarbonate solution (1 mL) was added and the mixture was stirred for 1 hour. Phases were separated and the aqueous phase was extracted with CH_2Cl_2 . The combined organic phase was dried over sodium bicarbonate and concentrated under vacuum to yield the target imine (566 mg, 1.93 mmol, 96%); IR (thin film) 3026, 2930, 2853, 1624, 1603, 1566, 1450, 1319, 1155, 1057, 853, 797, 777, 750 cm^{-1} ; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.40 (d, $J = 4.0$ Hz, 1H), 6.98 (s, 2H), 2.58 (s, 6H), 2.43 (m, 1H), 2.31 (s, 3H), 1.88–1.66 (m, 5H), 1.38–1.20 (m, 5H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 179.8, 143.7, 140.4, 132.1, 131.9, 44.0, 28.9, 26.2, 25.6, 23.1, 21.2; HRMS–ESI–TOF (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2\text{S}$, 294.1522; found, 294.1522.

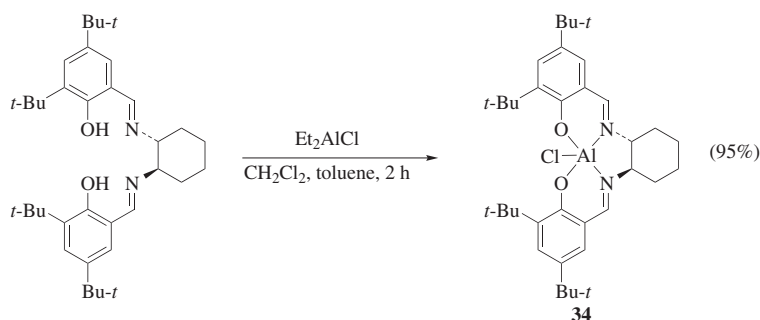


***N*-allyl-*N*-((4-*tert*-butylphenyl)(cyano)methyl)-2,2,2-trifluoroacetamide**
[General Procedure for Catalytic Enantioselective Strecker Reaction of Aldimines Using a Urea-Based Catalyst].³³ In a flame-dried 5-mL round-bottom flask equipped with a stirring bar, catalyst **28** (5 mg, 2 mol%, 0.008 mmol) and toluene (1.6 mL) were combined. The substrate (0.4 mmol, 200 mM final concentration) was added by syringe. The reaction mixture was stirred at ambient temperature until the catalyst completely dissolved. The reaction flask was cooled to -70° by means of a constant temperature bath and then a toluene solution of HCN (1.54 M, 340 μL , 0.52 mmol, 1.3 eq) was added slowly by syringe. After 20 hours, the reaction mixture was left to warm to ambient temperature and quenched with trifluoroacetic anhydride (103 μL , 0.73 mmol, 1.5 eq). The solvents were removed under vacuum and the resulting residue was purified by flash chromatography (hexanes/ $\text{CH}_2\text{Cl}_2 = 3 : 2$) to afford the Strecker adduct as a clear oil (89% yield, 97% ee); HPLC (Chiralcel AD, 0.6% *i*-PrOH/hexane, 1 mL/min) $t_r = 9.0$ min (major), $t_r = 11.4$ min (minor); $[\alpha]_D^{23} -61.4^\circ$ (c 1.0, CH_2Cl_2); IR (thin film) 2966, 1704, 1213, 1154 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.47 (d, $J = 8.2$ Hz, 2H), 7.37 (d, $J = 8.2$ Hz, 2H), 6.60 (s, 1H), 5.69 (m, 1H), 5.21 (d, $J = 10.4$ Hz, 1H), 5.15 (d, $J = 17.2$ Hz, 1H), 4.16 (dd, $J = 4.7, 17.0$ Hz, 1H), 3.92 (dd, $J = 6.2, 17.0$ Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 153.5, 131.2, 127.7, 127.0, 126.3, 120.1, 117.4, 115.4, 49.5, 48.4, 34.7, 31.1; HRMS (m/z): M^+ calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}$, 324.1449; found, 324.1436.



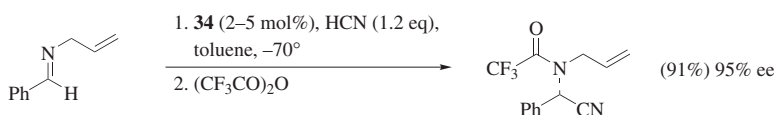
***N*-(Mesitylenesulfonyl)- α -(cyano)cyclohexylmethylamine [General Procedure for the Catalytic Enantioselective Strecker Reaction of Aldimines Using a Phase-Transfer Catalyst].⁶⁸**

A mixture of the starting imine (58.7 mg, 0.20 mmol), chiral ammonium iodide catalyst **33** (2.6 mg, 0.002 mmol) in toluene (1 mL), and H₂O (3 mL) was cooled to 0° and an aqueous KCN solution (2 M, 150 μ L, 0.3 mmol) was added dropwise. The reaction mixture was stirred vigorously at this temperature for 2 hours, saturated aqueous NH₄Cl solution was added, and the mixture was extracted with CH₂Cl₂. The combined extracts were dried over Na₂SO₄. Evaporation of solvents and purification of the crude products by flash column chromatography on silica gel (EtOAc/hexane = 1 : 4) gave the title compound (57.0 mg, 0.178 mmol, 89% yield, 95% ee); HPLC (Daicel Chiralpak AD-H, 2-propanol/hexane = 1 : 10, 0.5 mL/min, λ = 254 nm), t_r = 13.3 min (R) and 14.7 min (S); $[\alpha]_D^{29}$ - 18.9° (c 1.00, CHCl₃, 95% ee); IR (thin film) 3275, 3028, 2930, 2855, 2253, 1602, 1566, 1450, 1330, 1157, 1091, 1057, 904, 852, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.99 (s, 2H), 5.37 (d, J = 9.1 Hz, 1H), 3.92 (dd, J = 6.7, 9.1 Hz, 1H), 2.65 (s, 6H), 2.31 (s, 3H), 1.86-1.67 (m, 6H), 1.29-1.06 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 143.0, 139.0, 132.7, 132.1, 116.5, 49.5, 41.2, 29.0, 28.4, 25.7, 25.4, 25.3, 23.0, 21.1; HRMS-ESI-TOF (m/z): $[M + Na]^+$ calcd for C₁₇H₂₄N₂O₂SNa, 343.1454; found, 343.1451.



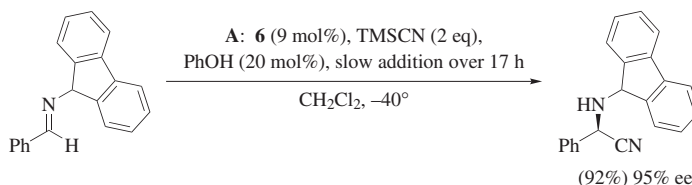
Chiral (Salen)Al(III) Complex [Catalyst Preparation].⁶⁹ In a flame-dried 100-mL round-bottom flask equipped with a stir bar were combined and stirred salen ligand (1.52 g, 2.78 mmol) and CH₂Cl₂ (20 mL, freshly distilled from CaH₂). A toluene solution of diethylaluminum chloride (1.8 M, 1.54 mL, 2.78 mmol) was added slowly to the stirring solution at ambient temperature. After stirring for 2 hours, the solvents were removed under vacuum and the resulting yellow solid was rinsed with 50 mL of hexane. The solid was dried

under vacuum to yield catalyst **34** (1.59 g, 95% yield) as a yellow solid, mp $>350^{\circ}$ (dec); IR (KBr) 2966, 2953, 2867, 1640, 1544, 848 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6) δ 7.84 (s, 2H), 7.77 (s, 2H), 7.61 (s, 2H), 3.51 (m, 2H), 1.91 (s, 18H), 1.39 (s, 18H), 1.36 (m, 4H), 0.59 (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 162.7, 141.2, 139.3, 131.4, 128.7, 128.4, 118.7, 64.6 (broad), 35.9, 34.4, 31.6, 30.0, 28.2, 24.1. Anal. Calcd for $\text{C}_{36}\text{H}_{52}\text{AlClN}_2\text{O}_2$: C, 71.20; H, 8.42; Al, 4.44; Cl, 5.84; N, 4.61. Found: C, 71.05; H, 8.63; Al, 4.49; Cl, 5.73; N, 4.56.



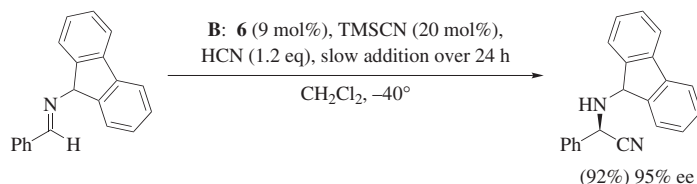
(S)-N-Allyl-N-(phenyl(cyano)methyl)-2,2,2-trifluoroacetamide [General Procedure for the Catalytic Enantioselective Strecker Reaction of Aldimines Using an Aluminum Catalyst].⁶⁹

In a flame-dried 5-mL round-bottom flask equipped with a stir bar, **34** (12 mg, 5 mol%, 0.02 mmol) and toluene (1.4 mL) were combined. The reaction mixture was stirred at ambient temperature until the catalyst had completely dissolved. The reaction flask was cooled to -70° by means of a constant-temperature bath, and a toluene solution of HCN was added (0.85 M, 690 μL , 0.59 mmol, 1.2 eq). After 5 minutes, N-allyl benzylidene (71 mg, 0.49 mmol) was added in one portion by syringe. After 15 hours, the reaction was quenched with trifluoroacetic anhydride (103 μL , 0.73 mmol, 1.5 eq) and left to warm to ambient temperature. The solvents were removed under vacuum, and the resulting residue was purified by flash chromatography (hexane/ CH_2Cl_2 = 3 : 2) to afford the title product as a clear oil (119 mg, 91% yield, 95% ee); Chiral GC (γ -TA, 112° for 23 min, $3^{\circ}/\text{min}$ to 123°) t_r = 21.5 min (major), t_r = 23.9 min (minor); $[\alpha]_D^{23}$ 57.7 $^{\circ}$ (c 1.0, CH_2Cl_2); IR (thin film) 2936, 2249, 1701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.45 (m, 5H), 6.65 (s, 1H), 5.66 (m, 1H), 5.19 (d, J = 10.2 Hz, 1H), 5.13 (d, J = 17.0 Hz, 1H), 4.15 (dd, J = 4.7, 17.0 Hz, 1H), 3.91 (dd, J = 6.0, 17.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.9 (q, J = 38 Hz), 131.1, 130.1, 130.0, 129.4, 127.8, 120.3, 117.5, 115.2, 49.8, 48.6; HRMS (m/z): $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$, 286.1167; found, 286.1163.

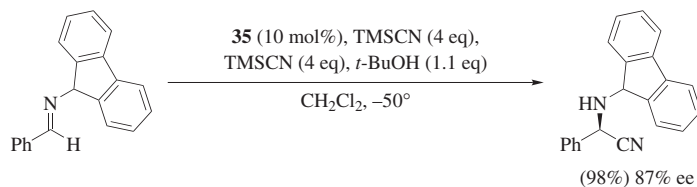


N-(9-Fluorenylamino)phenylacetonitrile [General Procedure for the Catalytic Enantioselective Strecker Reaction of Aldimines Using an Aluminum Catalyst: Condition A].^{26,27} The chiral substituted BINOL ligand precursor (13 mg, 18 μmol) was placed in a flame-dried flask and dissolved in CH_2Cl_2

(0.5 mL). To this solution was added a hexane solution of diethylaluminum chloride (0.96 M, 17 μ L, 16 μ mol) under argon. The resulting mixture was stirred at room temperature for 1 hour to give a clear solution of the BINOL-derived catalyst **6**. To the thus-prepared catalyst solution, a solution of the starting fluorenyl imine (0.17 mmol) in CH_2Cl_2 (0.6 mL) was added at -40° , followed by the addition of TMSCN (45 μ L, 0.34 mmol). After 30 minutes, a solution of phenol (3 μ , 34 μ mol) in CH_2Cl_2 (0.2 mL) was slowly added over 17 hours. The reaction mixture was stirred for an additional 44 hours. The reaction was quenched with aqueous saturated NaHCO_3 , and the mixture was diluted with Et_2O . The organic layer was separated, and the water layer was extracted with Et_2O . The combined organic layers were washed with water and dried over Na_2SO_4 . Further purification was performed by flash column chromatography on silica gel to afford the target fluorenyl aminonitrile (92% yield, 95% ee); HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 90 : 10, 1.0 mL/min) t_r = 13.3 min and 25.0 min; $[\alpha]_D^{24} - 14.0^\circ$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 7.78–7.68 (m, 3H), 7.53–7.26 (m, 10H), 5.14 (s, 1H), 4.57 (s, 1H), 2.34 (bs, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 143.6, 143.5, 141.1, 140.7, 135.8, 129.01, 128.98, 128.9, 128.8, 127.6, 127.4, 125.7, 125.0, 120.2, 120.1, 119.6, 62.2, 50.3.



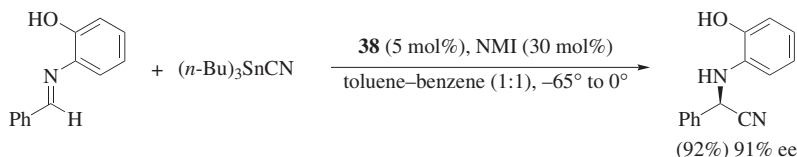
***N*-(9-Fluorenylamino)phenylacetonitrile [General Procedure for the Catalytic Enantioselective Strecker Reaction of Aldimines Using an Aluminum Catalyst: Condition B].**^{26,27} To a CH_2Cl_2 solution (1.0 mL) of catalyst **6** (33 μ mol) prepared as described above, a solution of the starting imine (0.352 mmol) in CH_2Cl_2 (1.0 mL) and TMSCN (70 μ mol) were added at -40° . To this mixture, a solution of HCN (0.422 mmol) in CH_2Cl_2 (0.26 mL) was slowly added over 24 hours. After 12 hours (total 36 hours), the reaction was worked up as described above to yield the title compound in 92% yield and 95% ee.



***N*-(9-Fluorenylamino)phenylacetonitrile [General Procedure for Catalytic Enantioselective Strecker Reaction of Aldimines Using a Solid-Supported Aluminum Catalyst].**⁷³ To the corresponding swollen polymer-supported ligand (19.1 mg, loading level = 0.52 mmol/g, 10 mmol) in CH_2Cl_2

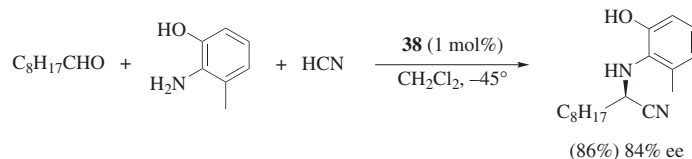
(0.4 mL), a hexane solution of diethylaluminum chloride (0.95 M, 10 μ L, 9.5 mmol) was added at ambient temperature, and the mixture was stirred for 1 hour to prepare catalyst **35**. The catalyst mixture was cooled to -50° , then the starting imine (27 mg, 0.1 mmol) in CH_2Cl_2 (0.25 mL), TMS-CN (54 μ L, 0.4 mmol), and *tert*-butanol (0.11 mmol) in CH_2Cl_2 (0.25 mL) were added successively with 10 minute intervals between additions. After 60 hours, saturated aqueous NaHCO_3 (1 mL) was added. The usual workup and purification by silica gel column chromatography afforded pure title compound in 98% yield and 87% ee.

Catalyst recycling experiments were performed as follows: Instead of quenching the reaction with NaHCO_3 , after the reaction was completed, dry Et_2O (five times the volume of CH_2Cl_2) was added and the reaction mixture was left for 3 hours. The supernatant containing the Strecker product was then decanted by syringe, and catalyst **35** was washed with dry Et_2O five times under an inert atmosphere. After drying the catalyst under reduced pressure for 30 minutes, CH_2Cl_2 , imine, TMS-CN, and *tert*-butanol were added at -50° to start the new cycle.

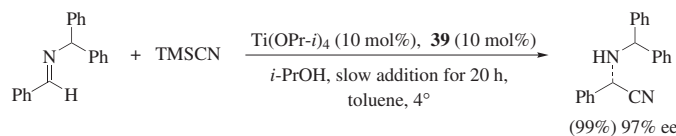


2-(2-Hydroxyphenyl)amino-2-phenylacetonitrile [General Procedure for the Catalytic Enantioselective Strecker Reaction of Aldimines Using a Zirconium Catalyst].^{51,75} To $\text{Zr}(\text{O}i\text{-Bu})_4$ (0.04 mmol) in toluene (0.25 mL) was added (*R*)-6-Br-BINOL (0.04 mmol), (*R*)-3-Br-BINOL (0.04 mmol), and *N*-methylimidazole (NMI; 0.12 mmol) in toluene (0.75 mL) at room temperature. The mixture was stirred for 1 hour, and then cooled to -65° to generate catalyst **38**. A benzene solution (1.0 mL) of the imine (0.4 mmol) and tributyltin cyanide (0.44 mmol) were added. The mixture was stirred and warmed from -65° to 0° over 12 hours, and then saturated aqueous NaHCO_3 was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 . After the usual workup, the crude product was chromatographed on silica gel to give the desired adduct (92%, 91% ee); HPLC (Daicel Chiralcel OD, hexane/isopropyl alcohol = 9 : 1, 1.0 mL/min) t_r = 40.0 min (major) and 49.7 min (minor); ^1H NMR (CDCl_3) δ 7.61–7.43 (m, 6H), 6.93–6.72 (m, 4H), 5.40 (d, 1H, J = 7.2 Hz), 4.43 (br, 1H); ^{13}C NMR (CDCl_3) δ 144.5, 134.0, 133.3, 129.5, 129.3, 127.2, 121.5, 120.7, 118.4, 114.9, 114.2, 50.6.

Since some of the products from this method were unstable, they were characterized after methylation of the phenolic OH group as follows: The product was treated with 20% MeI– Me_2CO (5 mL) and K_2CO_3 (200 mg). After the mixture was stirred at room temperature for 6 hours, saturated aqueous NH_4Cl was added to quench the reaction. After extraction of the aqueous layer with CH_2Cl_2 , the crude product was purified by chromatography on silica gel to afford the corresponding methylated product (quantitative yield).

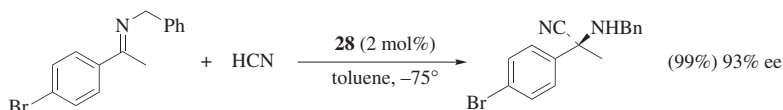


1-(2-Hydroxy-6-methylphenyl)aminononane-1-carbonitrile [General Procedure for the Catalytic Enantioselective Three-Component Strecker Reaction Using a Zirconium Catalyst].⁵¹ To a CH_2Cl_2 solution (3.0 mL) of (*R*)-6-Br-BINOL (0.04 mmol), (*R*)-3-Br-BINOL (0.04 mmol), and *N*-methylimidazole (0.12 mmol) was added a CH_2Cl_2 solution (1.0 mL) of $\text{Zr}(\text{O}i\text{Bu}-t)_4$ (0.04 mmol) at room temperature. After the mixture was stirred for 1 hour, a CH_2Cl_2 solution (0.2 mL) of HCN (0.8 mmol) was added at 0° , and the mixture was further stirred for 3 hours at the same temperature. The resulting solution was then added to a mixture of nonaldehyde (0.4 mmol) and 2-amino-3-methylphenol (0.4 mmol) in CH_2Cl_2 (1 mL) at -45° . After the mixture was stirred for 12 hours, HCN was added if the reaction was not yet completed. Saturated aqueous NaHCO_3 was then added to quench the reaction, and after the usual workup, the crude product was purified by chromatography on silica gel to give the desired adduct (86%, 84% ee); HPLC (Daicel Chiralpak AD, hexane/isopropyl alcohol = 19 : 1, 1.0 mL/min) t_r = 10.4 min (major) and 13.0 min (minor); ^1H NMR (CDCl_3) δ 6.93–6.70 (m, 3H), 4.00 (t, J = 7.3 Hz, 1H), 2.33 (s, 3H), 1.92 (dt, J = 7.3, 7.7 Hz, 2H), 1.70–1.20 (m, 12H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (CDCl_3) δ 150.1, 134.5, 130.6, 125.2, 123.0, 120.4, 113.4, 49.7, 34.2, 31.7, 29.1, 29.0, 25.6, 22.6, 17.7, 14.0; HRMS (m/z): M^+ calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}$, 274.2047; found, 274.2045.



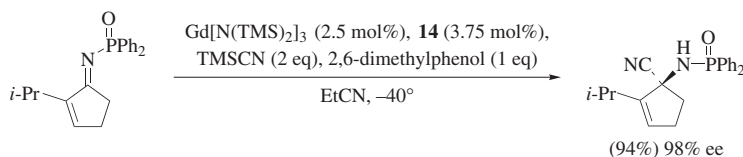
2-Benzhydrylamino-2-phenylacetonitrile [General Procedure for the Catalytic Enantioselective Strecker Reaction Using a Titanium Catalyst].²⁸ The reaction was set up inside of a glove box under a nitrogen atmosphere. Chiral ligand **39** (49 mg, 0.10 mmol) was placed into a flame-dried round-bottomed flask, and dissolved in toluene (5 mL). The flask was charged with a toluene solution of $\text{Ti}(\text{OPr}-i)_4$ (0.5 M, 0.2 mL, 0.1 mmol), and the yellow solution was stirred for 10 minutes at 22° . Subsequently, *N*-diphenylmethylbenzalimine (271 mg, 1.0 mmol) was added. The reaction vessel was capped with a septum, sealed with teflon tape, removed from the glove box, and placed in a room maintained at 4° . TMSCN (267 μL , 2.0 mmol) was added to the stirred solution. Isopropyl alcohol (153 μL , 2.0 mmol) in toluene (2 mL) was added over 20 hours with additional stirring for 10 hours. The crude reaction mixture was passed through a plug of silica with CH_2Cl_2 (5 mL) and concentrated under vacuum. The crude reaction mixture showed 99% conversion and 97% ee by HPLC

(Chiralpak AD). The pale yellow solid was recrystallized from hexane/CH₂Cl₂ (5:1) to afford the title compound (228 mg, 82%, >99% ee); [α]²⁴_D – 64.2° (c 5.0, CHCl₃); IR (CCl₄) 3327, 3087, 3069, 3031, 2848, 2231, 1948, 1879, 1810, 1608, 1501, 1451, 1187, 929 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.58–7.20 (m, 15H), 5.24 (s, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 2.14 (d, *J* = 12.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 243.4, 242.7, 235.6, 129.7, 129.6, 129.4, 128.6, 128.4, 128.1, 127.9, 127.7, 119.4, 66.2, 53.0; HRMS (*m/z*): [M + H]⁺ calcd for C₂₁H₁₈N₂, 299.1548; found, 299.1549. Anal. Calcd for C₂₁H₁₈N₂: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.22; H, 6.19; N, 9.28.



2-Benzylamino-2-(4-bromophenyl)propionitrile [General Procedure for Asymmetric Strecker Reaction of Ketimines Using a Urea Catalyst].³⁸

A 10-mL round-bottom flask equipped with a stir bar was charged with catalyst **28** (3.7 mg, 0.006 mmol, 0.02 eq), toluene (2 mL), and the starting ketimine (0.3 mmol). The reaction mixture was cooled to –75° by means of a constant temperature bath. In a separate 2-mL flask equipped with a stir bar, toluene (1 mL) and TMSCN (50 μ L, 1.25 eq) were combined. After cooling the solution to 5°, MeOH (15 μ L, 1.25 eq) was added. The solution was stirred for 2 hours at 5°, cooled to –78°, and then added to the reaction flask by syringe. When conversion of the starting material exceeded 99% as monitored by either ¹H NMR or HPLC, the solvents were removed under vacuum. The crude product was obtained as a solid (quantitative as a mixture with catalyst, 93% ee). Recrystallization from hexanes afforded pure title product as white needles (76% overall yield, >99.9% ee), mp 79.9–80.1°; HPLC (Chiralcel OD, *i*-PrOH/hexanes (3%), 1 mL/min) *t*_r = 15.9 min (major), *t*_r = 19.5 min (minor); [α]²³_D – 58.6° (c 1.0, CH₂Cl₂); IR (thin film) 3323, 2224 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 6 Hz, 2H), 7.59 (d, *J* = 6 Hz, 2H), 7.42–7.26 (m, 5H), 3.93 (d, *J* = 10 Hz, 1H), 3.58 (m, 1H), 2.02 (d, *J* = 5 Hz, 1H), 1.80 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 139.4, 139.1, 132.4, 128.9, 128.6, 127.8, 127.8, 123.0, 121.2, 60.4, 49.8, 31.5; EI–HRMS (*m/z*): M⁺ calcd for C₁₆H₁₅BrN₂, 314.0418; found, 314.0414.

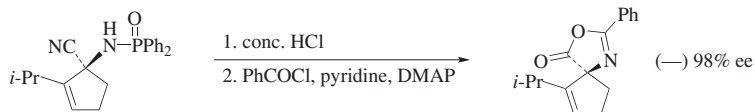


***N*-[1-Cyano-2-isopropylcyclopent-2-en-1-yl]-*P,P*-diphenylphosphinic Amide [General Procedure for the Asymmetric Strecker Reaction of Ketimines Using a Gadolinium Catalyst].⁸⁶**

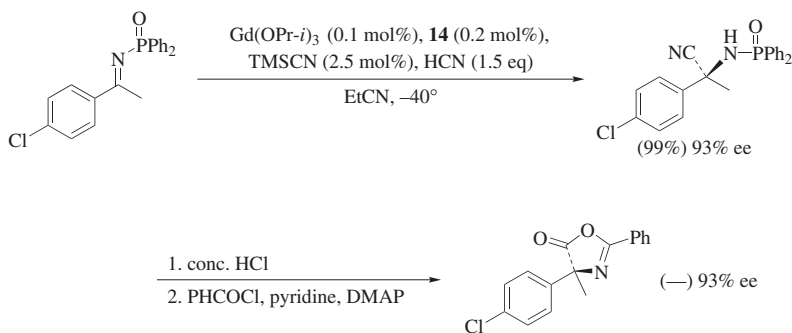
A solution of tris[*N,N*-bis(trimethylsilyl)]

amide]gadolinium in THF (0.2 M, 2.0 mL, 0.40 mmol) was added to a solution of ligand **14** (276 mg, 0.6 mmol) in THF (16 mL) at 4°, and the mixture was stirred at 50° for 1 hour. The solvent was evaporated, and the residue was dried under vacuum for 2 hours at room temperature. The resulting amorphous material was dissolved in propionitrile (18.7 mL), cooled to -40°, and TMSCN (4.3 mL, 32 mmol) and 2,6-dimethylphenol (1.95 g, 16 mmol) in THF (6 mL + 2 mL for wash) were added. The mixture was stirred for 0.5 hours at -40°, the imine substrate (5.2 g, 16 mmol) was added, and the reaction mixture was stirred for about 2.5 days at -40°. Silica gel (50 g) was added at -40° to quench the reaction. (*Caution! HCN generation! The reaction was quenched in a well-ventilated hood, and the generated HCN was trapped into a saturated NaHCO₃ bubbler.*). The slurry was filtered and the solid washed with a mixture of CH₂Cl₂ (400 mL) and MeOH (20 mL). The combined filtrate was concentrated under vacuum. The solid residue was partially purified by flash column chromatography (EtOAc/hexane = 2 : 1 to EtOAc/MeOH = 20 : 1) to afford the expected product as a white solid (5.9 g) containing chiral ligand **14**. To remove ligand **14**, toluene (117 mL) was added to the mixture (5.9 g), the mixture was warmed to 80°, and to the resulting solution hexane (47 mL) was added. The solution was cooled gradually to room temperature, and the precipitate was filtered off to afford the pure amide product (4.6 g) as a white solid. The filtrate was concentrated under vacuum and toluene (30 mL) was again added at 80°, followed by the addition of hexane (12 mL). After gradually cooling to room temperature, the precipitate was filtered to afford an additional crop of amide product (0.7 g). These two crops were combined, and the pure title product was obtained as a white solid [5.3 g, 94% yield, 98% ee (unaffected by the washing process)], mp 132–133°; [α]_D²³ + 12.9° (c 0.51, CHCl₃); IR (neat) 2230, 1590, 1437, 894 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.56–7.44 (m, 6H), 5.77 (m, 1H), 3.24 (d, *J* = 5.8 Hz, 1H), 2.73–2.69 (m, 1H), 2.59 (sept, *J* = 8.2 Hz, 1H), 2.47–2.44 (m, 1H), 2.40–2.34 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.5, 133.6, 132.5, 132.5, 132.4, 132.2, 131.4, 131.3, 131.1, 129.8, 128.8, 128.7, 128.7, 128.6, 120.4, 62.2, 40.2, 29.4, 26.9, 22.9, 22.7; ³¹P NMR (CDCl₃) δ 20.9; LRMS–FAB(*m/z*): [M + Na]⁺ 373; HRMS–FAB (*m/z*): [M + H]⁺ calcd for C₂₁H₂₄N₂OP, 351.1621; found, 351.1635.

Chiral ligand **14** was recovered as follows: The filtrate solution containing the ligand was evaporated, and concentrated aqueous HCl (20 mL) was added to the residue. The mixture was heated at 100° for 5 hours and poured into water (50 mL). Ligand **14** was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (30 mL), dried (Na₂SO₄), and concentrated. Pure ligand **14** was recovered in 90% yield through silica gel column chromatography (EtOAc/hexane = 1 : 1).

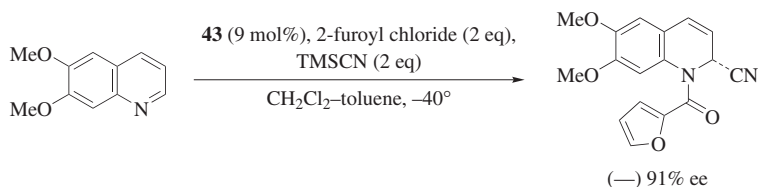


The enantiomeric excess of the Strecker product was determined by its conversion to the corresponding oxazoline according to the scheme above. Concentrated HCl (1 mL) was added to the cyclopentenyl amide product (10 mg), and the mixture heated at 100° for 5 hours. After cooling to room temperature, the reaction mixture was concentrated under vacuum. Pyridine (0.5 mL), benzoyl chloride (20 μ L), and 4-*N,N*-dimethylaminopyridine (DMAP, 5 mg) were added at room temperature. After stirring for 1 hour, the reaction mixture was poured into saturated aqueous NH_4Cl (5 mL). The products were extracted with EtOAc (2 \times 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by silica gel preparative TLC (EtOAc/hexane = 1 : 4) gave the oxazoline in 98% ee. The enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel OJ-H, *i*-PrOH/hexane = 1 : 99, 1.0 ml/min) t_r = 6.3 min (minor) and 7.2 min (major); $[\alpha]_D^{23} +1.5^\circ$ (c 0.95, CHCl_3); IR (neat) 3436, 2965, 1813, 1650 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.03–7.99 (m, 2H), 7.58–7.45 (m, 3H), 5.92 (brt, J = 2.3 Hz, 1H), 2.68–2.55 (m, 2H), 2.44–2.37 (m, 1H), 2.35–2.28 (m, 1H), 2.18–2.09 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 180.6, 160.4, 148.2, 132.7, 130.5, 128.8, 127.9, 126.0, 81.4, 36.8, 30.6, 27.5, 22.2, 22.2; LRMS–ESI (m/z): $[\text{M} + \text{Na}]^+$ 278.0.



4-(4-Chlorophenyl)-4-methyl-2-phenyl-4*H*-oxazol-5-one [General Procedure for the Catalytic Enantioselective Strecker Reaction of Ketimines Using a Gadolinium Catalyst: Combination of TMSCN and HCN].⁴¹ A THF solution of gadolinium triisopropoxide (0.2 M, 18.8 μ L, 3.8 μ mol) was added to a solution of ligand **14** (3.5 mg, 7.6 μ mol) in THF (75 μ L) in an ice bath. The mixture was stirred for 40 minutes at 45°, and then the solvent was evaporated. After drying the resulting pre-catalyst under vacuum (5 mmHg) for 1 hour, the substrate ketimine (1.33 g, 3.8 mmol) was added as a solid in one portion. Propionitrile (1 mL) was added at -40°, and after 30 minutes, TMSCN (12.5 μ L,

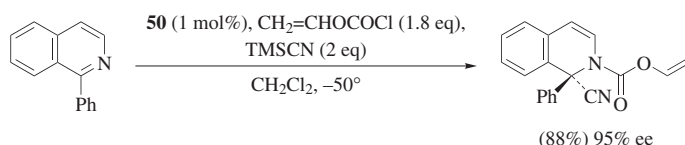
0.094 mmol) was added. After 5 minutes, a propionitrile stock solution of HCN (4 M, 1.4 mL, 5.6 mmol) was added to start the reaction. After 54 hours at -40° the reaction was complete, and silica gel was added. The mixture was carefully concentrated until no HCN gas remained as determined by monitoring with an HCN sensor. The silica gel was removed by filtration, and the filtrate was washed with MeOH/CHCl₃ (1 : 9). The combined liquids were removed by evaporation, and the resulting residue was purified by silica gel column chromatography to give the diphenylphosphinic amide intermediate (99% yield). The enantiomeric excess of the product was determined to be 93% after converting to the corresponding oxazoline, 4-(4-chlorophenyl)-4-methyl-2-phenyl-4*H*-oxazol-5-one, as described above. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 499 : 1, 1.0 ml/min) t_r = 18.7 min (minor) and 22.4 min (major); $[\alpha]^{22}_D +120.5^{\circ}$ (c 1.37, CHCl₃); IR (neat) 1820, 1656, 1007 cm⁻¹; ¹H NMR (CDCl₃) δ 8.09 (d, J = 8.3 Hz, 2H), 7.62–7.50 (m, 5H), 7.36 (d, J = 8.5 Hz, 2H), 1.86 (s, 3H); ¹³C NMR (CDCl₃) δ 178.8, 160.4, 137.3, 134.3, 133.0, 128.8, 128.1, 126.9, 125.7, 70.2, 27.3; EIMS (m/z): M⁺ 285; EI–HRMS (m/z): M⁺ calcd for C₁₆H₁₂ClNO₂, 285.0557; found, 285.0564.



***N*-(2-Furoyl)-2-cyano-6,7-dimethoxy-1,2-dihydroquinoline [General Procedure for the Catalytic Enantioselective Reissert Reaction of Quinolines].^{47,48}**

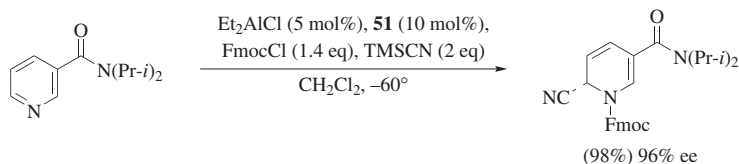
Diethylaluminum chloride in hexane (30 μ L, 0.029 mmol) was added at ambient temperature to a solution of the corresponding ligand (22 mg, 0.029 mmol) in CH₂Cl₂ (2.5 mL) and the resulting solution was stirred for 1 hour. This catalyst solution of **43** was cooled to -40° , and a solution of 6,7-dimethoxyquinoline (60.5 mg, 0.32 mmol) in CH₂Cl₂ (0.5 mL) was added, followed by the addition of 2-furoyl chloride (63 μ L, 0.64 mmol). After adding toluene (2.5 mL), TMSCN (85 μ L, 0.64 mmol) in toluene (0.5 mL) was added slowly over 24 hours at -40° . A saturated aqueous solution of NaHCO₃ was added after 40 hours, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated NaCl and dried over Na₂SO₄. Evaporation of the solvent and purification of the resulting crude product by silica gel column chromatography (EtOAc/hexane = 1 : 4) gave pure title compound in 91% ee; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 70 : 30, 1.0 mL/min) t_r = 15.7 and 20.8 min; $[\alpha]^{23}_D +267^{\circ}$ (c 1.0, CHCl₃); IR (KBr) 3447, 2234, 1655 cm⁻¹; ¹H NMR (CDCl₃) δ 7.41 (m, 1H), 6.92 (d, J = 3.4 Hz, 1H), 6.78–6.72 (m, 2H), 6.47 (m, 1H), 6.43 (brs, 1H), 6.10 (d, J = 6.7 Hz, 1H), 5.96 (dd, J = 6.7, 9.1 Hz, 1H), 3.91 (s, 3H), 3.62 (s, 3H); ¹³C NMR (CDCl₃) δ 158.2, 148.9, 147.4, 146.3, 145.1, 129.2, 127.3, 112.8, 117.7, 116.0, 111.9, 109.4, 107.7, 56.2, 56.0, 42.5;

EIMS (m/z): M^+ 310; EI-HRMS (m/z): M^+ calcd for $C_{17}H_{14}N_2O_4$, 310.0943; found 310.0957.



1-Cyano-1-phenyl-1,2-dihydroisoquinoline-2-carboxylic Acid Vinyl Ester [General Procedure for Generating Quaternary Stereocenters by Catalytic Enantioselective Reissert Reaction of Isoquinolines].⁴⁹

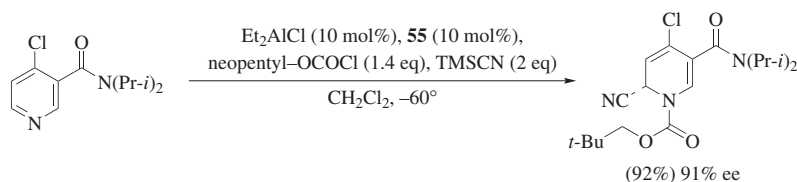
To a CH_2Cl_2 solution (3 mL) of ligand **50** (13.1 mg, 0.015 mmol), a hexane solution of trimethylaluminum (0.98 M, 15.3 μ L, 0.015 mmol) was added at ambient temperature and the resulting solution was stirred for 1 hour. A CH_2Cl_2 solution of freshly distilled triflic acid (0.0585 M, 250 μ L, 0.146 mmol, 97.5 mol% to trimethylaluminum) was then added and the mixture was stirred for 30 minutes. To the catalyst solution was added a solution of 1-phenylisoquinoline (308 mg, 1.5 mmol) in CH_2Cl_2 (2.5 mL) at -50° , followed by TMSCN (400 μ L, 3.0 mmol) and vinyl chloroformate (230 μ L, 2.7 mmol). After 48 hours, 5% aqueous NH_3 was added. The solution was extracted with CH_2Cl_2 and purified by silica gel column chromatography (hexane/EtOAc) to give the title product (88%, 95% ee); HPLC (Daicel Chiralpak AD, hexane/2-propanol = 98 : 2, 1.0 mL/min) t_r 12.1 min and 14.3 min; $[\alpha]_D^{25} +195^\circ$ (c 0.60, $CHCl_3$); IR (neat) 1737, 1652, 1495, 1453, 1382, 1323, 1259, 1194, 1143, 943, 876, 762, 695 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.62–7.60 (m, 2H), 7.37–7.28 (m, 3H), 7.22–7.03 (m, 5H), 5.83 (d, J = 8.2 Hz, 1H), 4.86 (d, J = 13.4 Hz, 1H), 4.55 (dd, J = 6.6, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 149.5, 142.2, 141.2, 130.3, 129.3, 128.8, 128.7, 128.4, 128.1, 126.9, 125.7, 125.0, 123.4, 117.7, 105.3, 98.2, 62.9; EIMS (m/z): M^+ 302; EI-HRMS (m/z): M^+ calcd for $C_{19}H_{14}N_2O_2$, 302.1055; found, 302.1055.



2-Cyano-5-diisopropylcarbamoyl-2H-pyridine-1-carboxylic Acid 9H-Fluorenylmethyl Ester [General Procedure for the Catalytic Enantioselective Reissert Reaction of Pyridine Derivatives].⁵⁰

Ligand **51** (0.02 mmol) was dried under reduced pressure for 1 hour, and dissolved in CH_2Cl_2 (0.5 mL). A hexane solution of diethylaluminum chloride (0.98 M, 10.2 μ L, 0.01 mmol) was added and the mixture stirred at room temperature for 1 hour. The resulting mixture was cooled to -60° , and a CH_2Cl_2 solution of *N,N*-diisopropylnicotine amide (0.4 M, 0.5 mL, 0.2 mmol), 9-fluorenylmethoxycarbonyl chloride (FmocCl,

2.8 mmol), and TMSCN (53.3 μ L, 4.0 mmol) were added successively. After the reaction was completed, water was added. The products were extracted three times with CH_2Cl_2 . The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to give the title product (98%, 96% ee); HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 9 : 1, 1.0 mL/min, λ 254 nm) t_r = 38.5 min, t_r = 42.1 min (minor); $[\alpha]_D^{20}$ -153.33° (c 0.93, CHCl_3); IR (neat) 3462, 3092, 2958, 1736, 1653, 1624, 1442, 1371, 1297, 1255, 1211 cm^{-1} ; ^1H NMR (DMSO-d_6 , 50°) δ 7.86 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 6.4 Hz, 2H), 7.41 (t, J = 7.3 Hz, 2H), 7.33 (t, J = 7.3 Hz, 2H), 6.53 (brd, 1H), 6.26 (d, J = 8.9 Hz, 1H), 5.98 (d, J = 5.8 Hz, 1H), 5.77 (t, J = 8.9 Hz, 1H), 4.74 (brd, 1H), 4.64 (brd, 1H), 4.40 (t, J = 5.8 Hz, 1H), 3.71 (m, 2H), 1.21 (brd, 12H); ^{13}C NMR (CDCl_3) δ 166.7, 152.0, 142.9, 142.8, 141.3, 128.0, 127.3, 124.7, 124.6, 120.2, 120.1, 115.7, 69.3, 46.8, 42.8, 21.0, 20.8; ESI-MS (m/z): $[\text{M} + \text{H}]^+$ 456, $[\text{M} + \text{Na}]^+$ 478; HRMS-FAB (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{30}\text{N}_3\text{O}_3$, 456.2287; found, 456.2285.



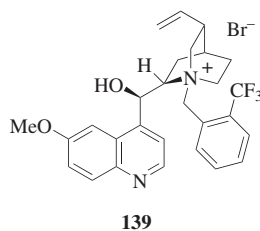
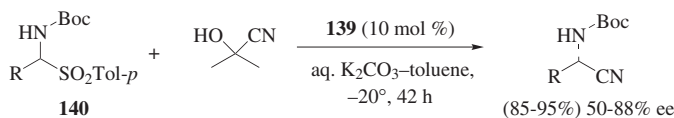
4-Chloro-2-cyano-5-diisopropylcarbamoyl-2H-pyridine-1-carboxylic Acid 2,2-Dimethylpropyl Ester [General Procedure for the Catalytic Enantioselective Reissert Reaction of a Halide-Substituted Pyridine Derivative].⁵⁰

Ligand **55** (0.02 mmol) was dried under reduced pressure for 1 hour, and dissolved in CH_2Cl_2 (1.5 mL). A hexane solution of diethylaluminum chloride (0.98 M, 20.4 μ L, 0.02 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was cooled to -60° , and 4-chloro-*N,N*-diisopropylnicotinamide in CH_2Cl_2 (0.4 M, 0.5 mL, 0.2 mmol), neopentyl chloroformate (2.8 mmol), and TMSCN (53.3 μ L, 4.0 mmol) were added successively. After the reaction was completed, water was added. The products were extracted three times with CH_2Cl_2 . The organic phase was washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to give the title compound (92% yield, 91% ee); HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH = 20 : 1, 1.0 mL/min, λ 254 nm) t_r = 24.4 min (major), t_r = 17.3 min (minor); $[\alpha]_D^{23}$ -175.0° (c 0.68, CHCl_3); IR (neat) 3452, 2076, 1634, 759 cm^{-1} ; ^1H NMR (DMSO-d_6 , 50°) δ 6.92 (s, 1H), 6.15 (d, J = 6.9 Hz, 1H), 5.97 (d, J = 6.9, 1H), 4.1-3.5 (brd, 2H), 4.0 (d, J = 10.3 Hz, 1H), 3.9 (d, J = 10.3 Hz, 1H), 1.27 (s, 12H), 0.96 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 162.7, 151.5, 128.8, 126.0, 123.5, 116.1, 112.0, 76.5, 50.8, 45.2, 44.4, 31.2, 25.9, 20.0; ESI-MS (m/z): $[\text{M} + \text{Na}]^+$ 304; HRMS-FAB (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{ClN}_3\text{O}_3$, 382.1897; found 382.1893.

ADDITIONAL CONTRIBUTIONS AFTER MANUSCRIPT SUBMISSION

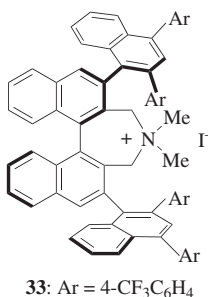
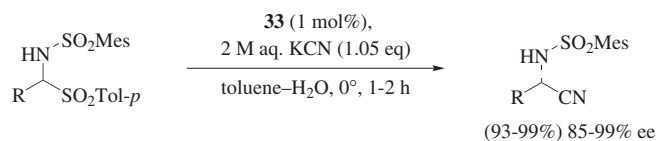
Due to high interest in the catalytic asymmetric Strecker reaction, several important papers have been published after this manuscript was submitted. In this section, the latest contributions in this field (from November 2006 to August 2007) are surveyed.¹⁸⁵

Quinine-derived quaternary ammonium salt **139** catalyzed an asymmetric Strecker reaction using α -amido sulfones **140** as aldimine precursors and acetone cyanohydrin as a cyanide source (Eq. 63).¹⁸⁶ Highly reactive aliphatic *N*-Boc imines were generated in situ in the presence of a stoichiometric base (aqueous K_2CO_3). Aliphatic substrates, including unstable linear aliphatic substrates, resulted in moderate to high enantioselectivity. Analogous reactions involving aromatic substrates, however, were not described.



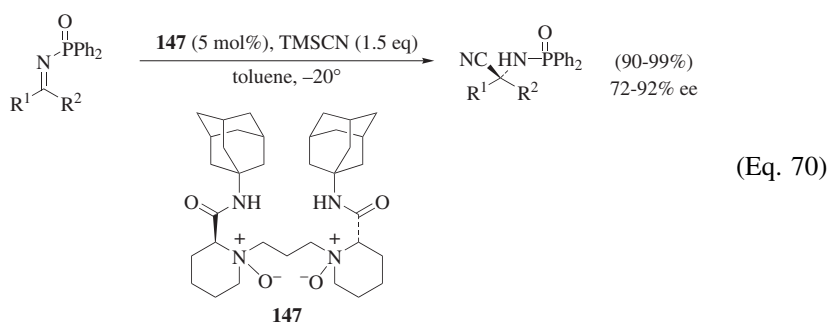
(Eq. 63)

A similar approach was reported using chiral phase-transfer catalyst **33** and KCN (1.05 eq) was used as a cyanide source (Eq. 64).¹⁸⁷ Chemical yields and enantioselectivities improved compared to the reactions starting from the pre-formed aldimines.⁶⁸

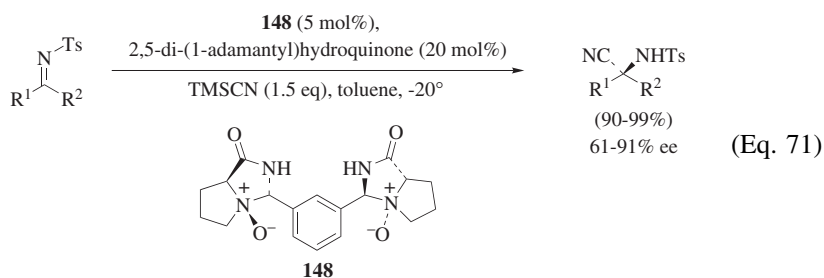


(Eq. 64)

Bis(pipercolic acid)-derived *N*-oxide catalyst **147** promotes an enantioselective Strecker reaction of *N*-phosphinoyl ketimines with high enantioselectivity (Eq. 70).¹⁹⁴ A dual activation transition state model is proposed, in which oxygen atoms of the *N*-oxide act as Lewis bases to activate TMSCN and an amide hydrogen atom acts as a Brønsted acid to activate the imine. A related organocatalyst **148** has been developed for a catalytic enantioselective Strecker reaction of *N*-tosyl ketimines (Eq. 71).¹⁹⁵ The enantioselectivity of catalyst **148** was in the moderate range.

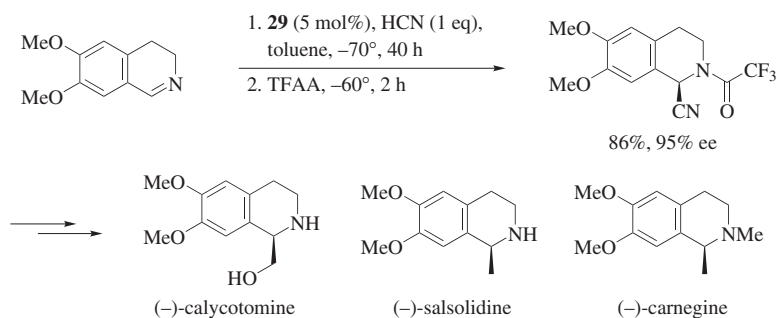


(Eq. 70)



(Eq. 71)

Jacobsen's catalytic asymmetric Strecker reaction was applied to the synthesis of several isoquinoline alkaloids, such as (–)-calycotomine, (–)-salsolidine, and (–)-carnegine. The chiral stereogenic center was constructed in high efficiency using the catalytic asymmetric Strecker reaction (Eq. 72).¹⁹⁶



(Eq. 72)

TABULAR SURVEY

The literature has been surveyed up to August 2007. The reactions in the Tables are arranged in order of increasing carbon number of the imines, excluding the protecting group of the nitrogen atom. The reactions of aldimines are listed in Table 1. The reactions of ketimines are listed in Table 2. The catalytic enantioselective Reissert reactions are listed in Table 3. The catalytic enantioselective Strecker reactions of aldimines and ketimines reported in the literature disclosed after submission of this manuscript (from November 2006 to August 2007) are listed in Table 4 and Table 5, respectively. Yields of the products are included in parentheses; (—) indicates that the yield was not reported. Enantiomeric excesses (ee) of the products are also listed.

The following abbreviations have been used in the Tables:

BINOL	binaphthol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
DAHQ	2,5-di-(1-adamantyl)hydroquinone
Flu	9-fluorenyl
Fm	fluorenylmethyl
fur	furyl
FmocCl	9-fluorenylmethoxycarbonyl chloride
HMDS	hexamethyldisilazide
Mes	mesityl (2,4,6-trimethylphenyl)
Mtr	4-methoxy-2,3,6-trimethylbenzenesulfonyl
Mts	2,4,6-trimethylphenylsulfonyl
naph	naphthyl
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
TADDOL	[5-(hydroxydiphenylmethyl)-2,2-dimethyl- [1,3]dioxolan-4-yl]-diphenylmethanol
<i>t</i> -Bu	<i>tert</i> -butyl
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
Tol	tolyl
Ts	<i>p</i> -toluenesulfonyl

CHART 1. CATALYTS AND LIGANDS USED IN TABLES

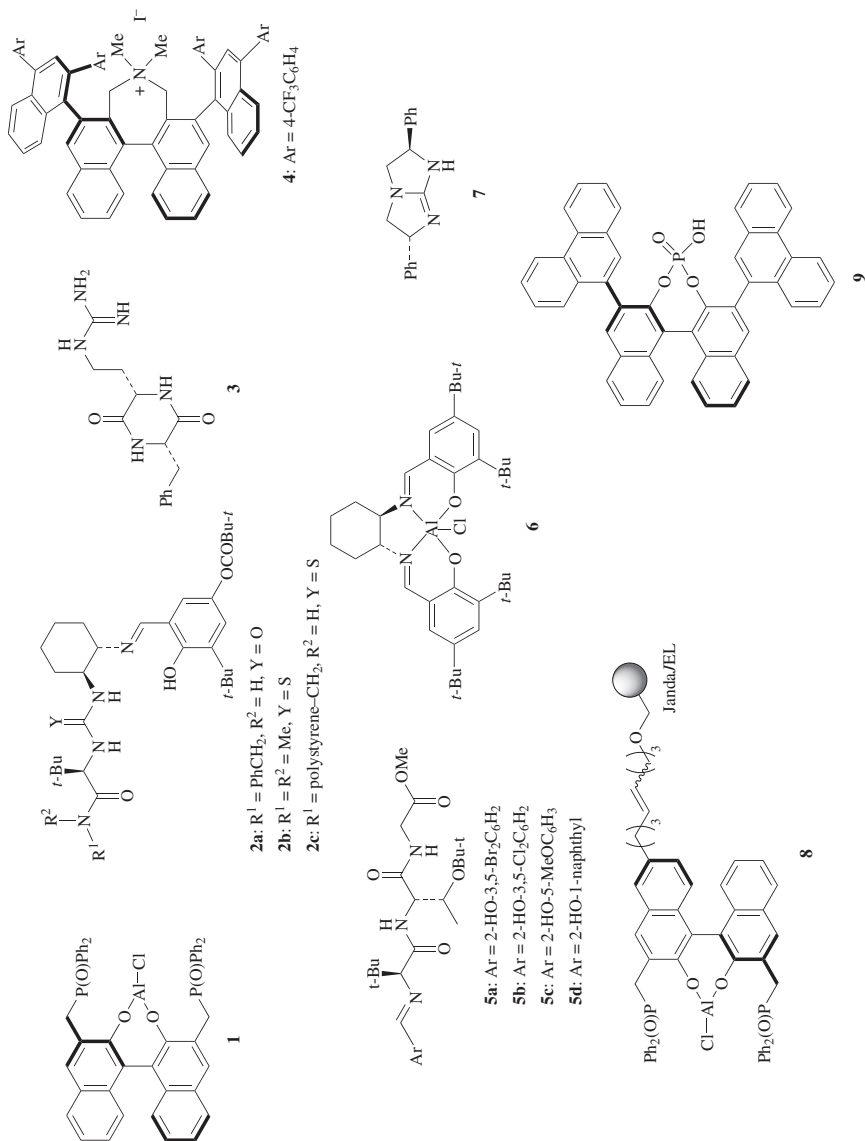
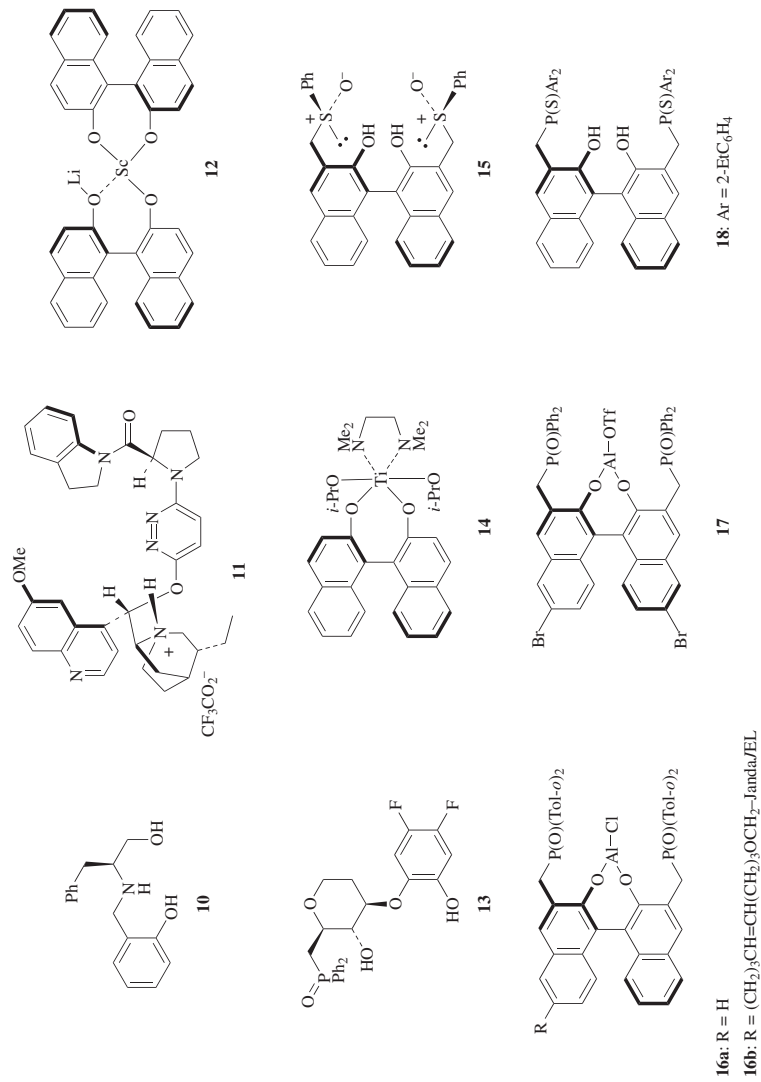


CHART 1. CATALYTS AND LIGANDS USED IN TABLES (Continued)



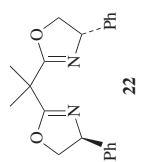
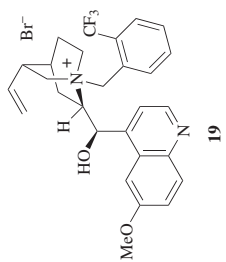
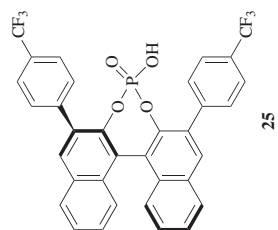
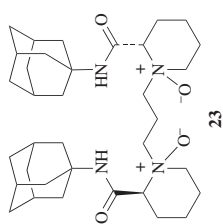
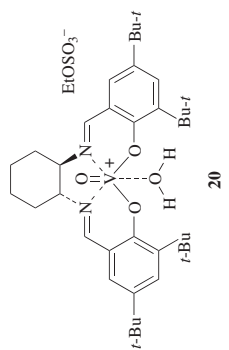
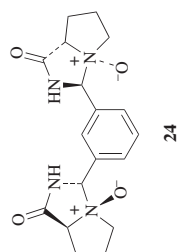
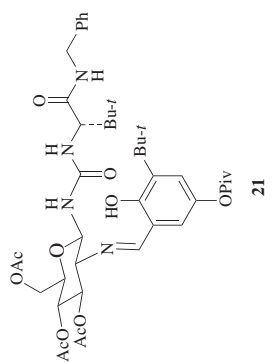


TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES

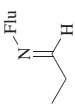
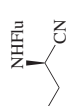
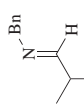
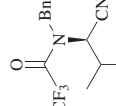
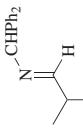
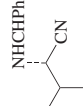
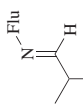
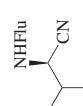
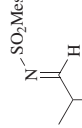
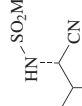
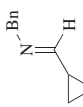
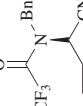
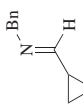
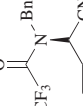
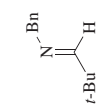
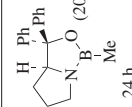
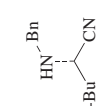
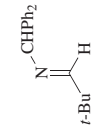
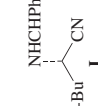
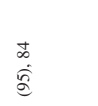

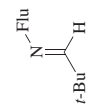
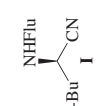
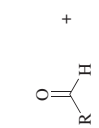
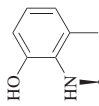
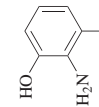
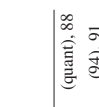
Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C ₃	TMSCN (2.0 eq), phenol (20 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 44 h	 (84), 70	26, 27
 C ₄	HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 20 h; then TFAA	 (74), 79	33
	HCN (2.0 eq), catalyst 3 (2 mol%), MeOH, -75°	 (81), <10	59
	TMSCN (2.0 eq), phenol (20 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 44 h	 (89), 72	26, 27
	HCN (1.2 eq, slow addition for 24 h), TMSCN (20 mol%), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 36 h	 1 (92), 71	26, 27
	2 M aq KCN (1.5 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 3 h	 (85), 93	68
	HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 20 h; then TFAA	 (89), 91	33

TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C_5	 HCN (1.5 eq), catalyst 3 (2 mol%), toluene, -25° , 24 h	 (82), 39	74
	HCN (2.0 eq), catalyst 3 (2 mol%), MeOH, -75°	 (80), 17	59
	HCN (2.0 eq), catalyst 7 (10 mol%), toluene, -40° , 22 h	 (95), 84	37
	TMSCN (2.0 eq), <i>n</i> -BuOH (1.5 eq, slow addition for 20 h), Ti(OP <i>i</i> -Pr) ₄ (10 mol%), ligand 5a (10 mol%), 1,1,1-trichloroethane, 4°	 (100), 85 ^o	28
	TMSCN (2.0 eq), phenol (20 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40° , 44 h	 (97), 78	26, 27
	HCN (1.2 eq, slow addition for 24 h), TMSCN (20 mol%), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40° , 36 h	 (98), 77	26, 27
 +	HCN (2.0 eq), Zr(OP <i>n</i> -Pr) ₄ (5 mol%), (<i>R</i>)-6-BINOL (5 mol%), (<i>R</i>)-3-BINOL (5 mol%), <i>N</i> -methylimidazole (15 mol%), CH ₂ Cl ₂ , -45°	 (88), 88 (94), 91	51

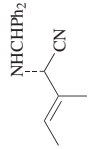
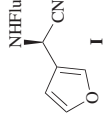

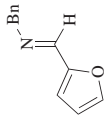
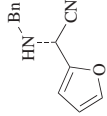
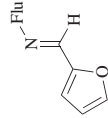
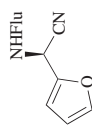
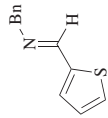
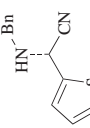
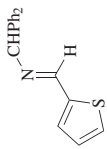
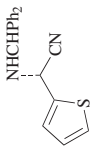
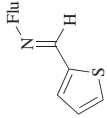
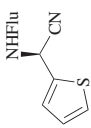
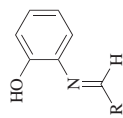
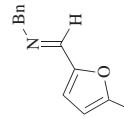
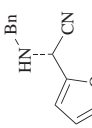
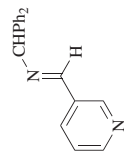
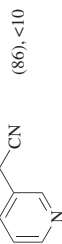
	TMSCN (2.0 eq), <i>n</i> -BuOH (1.5 eq, slow addition for 10 h), Ti(OPr- <i>i</i>) ₄ (15 mol%), ligand 5b (15 mol%), toluene, -20°		(86), 94	29
	TMSCN (2.0 eq), phenol (20 mol%), slow addition for 17 h), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 44 h		(92), 90	26, 27
	HCN (1.2 eq, slow addition for 24 h), TMSCN (20 mol%), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 36 h		1 (92), 87	26, 27
	TMSCN (4 eq), <i>t</i> -BuOH (1.1 eq), polymer-supported catalyst 8 (10 mol%), CH ₂ Cl ₂ , -50°, 66 h		1 (97), 86	73
	HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°		(84), 89	67
	HCN (2.0 eq), catalyst 3 (2 mol%), MeOH, -75°		(94), 32	59
	TMSCN (2.0 eq), 2-propanol (1.0 eq), Ti(OPr- <i>i</i>) ₄ (10 mol%), ligand 10 (10 mol%), toluene, 0°		1 (82), 91	77

TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

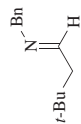
Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.						
 C ₅	TMSCN (2.0 eq), phenol (20 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 44 h	 (93), 79	26, 27						
	HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°	 (77), 95	67						
	TMSCN (2.0 eq), 2-propanol (1.0 eq), Ti(OPr- <i>i</i>) ₄ (10 mol%), ligand 10 (10 mol%), toluene, 0°	 (83), 98	77						
	TMSCN (2.0 eq), phenol (20 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 58 h	 (90), 89	26, 27						
 C ₆	(<i>n</i> -Bu) ₃ SnCN (1.1 eq), Zr(OBu- <i>i</i>) ₄ (10 mol%), (<i>R</i>)-6-BINOL (10 mol%), (<i>R</i>)-3-BINOL (10 mol%), <i>N</i> -methylimidazole (30 mol%), toluene-benzene, -65° to 0°	<table border="1" data-bbox="974 630 1071 840"> <thead> <tr> <th>R</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td><i>i</i>-Bu</td> <td>12 h</td> </tr> <tr> <td>2-thienyl</td> <td>—</td> </tr> </tbody> </table> (79), 83 (89), 92	R	Time	<i>i</i> -Bu	12 h	2-thienyl	—	51, 76
R	Time								
<i>i</i> -Bu	12 h								
2-thienyl	—								
	HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°	 (85), 92	67						



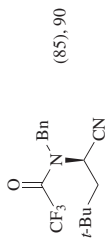
HCN (2.0 eq), catalyst **3** (2 mol%),
MeOH, -75°



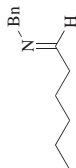
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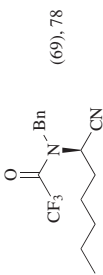
HCN (1.3 eq), catalyst **2a** (2 mol%),
toluene, -70°, 20 h; then TFAA



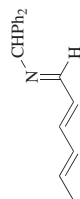
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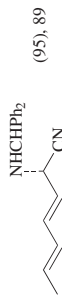
HCN (1.3 eq), catalyst **2a** (2 mol%),
toluene, -70°, 20 h; then TFAA



33

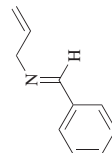


TMSCN (2.0 eq),
n-BuOH (1.5 eq, slow addition for 10 h),
Ti(OP*i*-Pr)₄ (15 mol%), ligand **5c** (15 mol%),
toluene, -20°

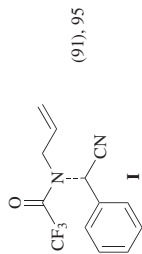


29

C₇

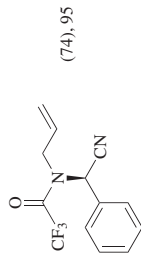


HCN (1.2 eq), catalyst **6** (5 mol%),
toluene, -70°, 15 h; then TFAA



69

HCN (1.3 eq), catalyst **2a** (2 mol%),
toluene, -70°, 20 h; then TFAA



33

I (95), 92

HCN (2.0 eq), catalyst **11** (10 mol%),
CH₂Cl₂, -70°, 36 h; then TFAA

64

TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	HCN (1.5 eq), toluene, -25°, 24 h	 (94), 71	74
	HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°	 (87), 89	67
	HCN (2.0 eq), catalyst 3 (2 mol%), MeOH, -25°	 (97), >99	59
	TMSCN (2.0 eq), 2-propanol (1.5 eq, slow addition for 20 h), Ti(OPr- <i>i</i>) ₄ (10 mol%), ligand 5c (10 mol%), toluene, 4°	I (99), 97 ^b	28
	TMSCN (2.0 eq), 2-propanol (1.0 eq), Ti(OPr- <i>i</i>) ₄ (10 mol%), ligand 10 (10 mol%), toluene, 0°	I (85), 96	77
	HCN (2.0 eq), catalyst 7 (10 mol%), toluene, -40°, 20 h	 (96), 86	37
	TMSCN (2.0 eq), phenol (20 mol%), slow addition for 17 h, catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 44 h	 (92), 95	26, 27

HCN (1.2 eq, slow addition for 24 h),
TMSCN (20 mol%), catalyst **1** (9 mol%),
CH₂Cl₂, -40°, 36 h

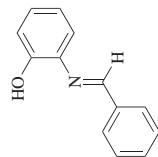
1 (92), 95

26, 27

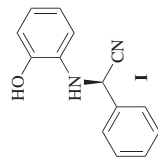
TMSCN (4 eq), *t*-BuOH (1.1 eq),
polymer-supported catalyst **8** (10 mol%),
CH₂Cl₂, -50°, 60 h

1 (98), 87

73

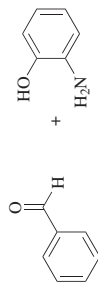


(*n*-Bu)₃SnCN (1.1 eq), Zr(OBu-*t*)₄ (10 mol%),
(*R*)-6-BINOL (10 mol%),
(*R*)-3-BINOL (10 mol%),
N-methylimidazole (30 mol%),
toluene-benzene, -65° to 0°, 12 h



(92), 91

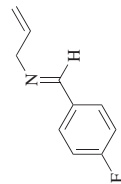
51, 75



HCN (2.0 eq), Zr(OBu-*t*)₄ (10 mol%),
(*R*)-6-BINOL (10 mol%),
(*R*)-3-BINOL (10 mol%),
N-methylimidazole (30 mol%), CH₂Cl₂, -45°

1 (80), 86

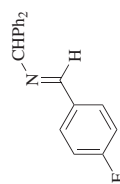
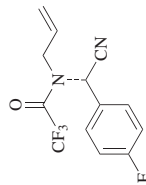
51



(96), 89

64

HCN (2.0 eq), catalyst **11** (10 mol%),
CH₂Cl₂, -70°, 24 h; then TFAA

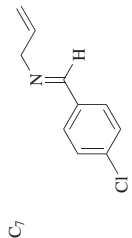
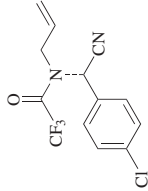
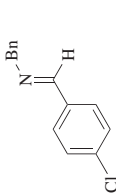
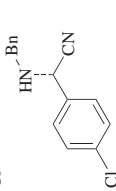
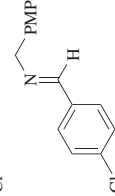
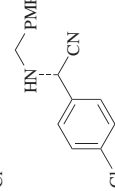
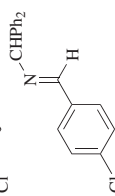
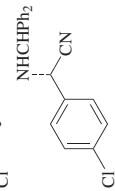
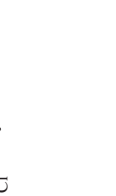
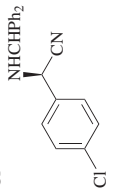
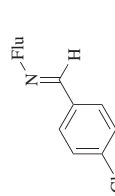
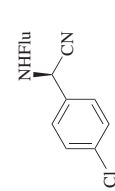
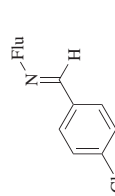
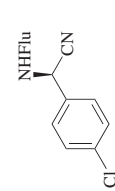


(97), 86

37

HCN (2.0 eq), catalyst **7** (10 mol%),
toluene, -40°, 23 h

TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C7	HCN (1.2 eq), catalyst 6 (5 mol%), toluene, -70°, 15 h; then TFAA	 (92), 81	69
	HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°	 (69), 85	67
	HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°	 (60), 86	67
	HCN (2.0 eq), catalyst 3 (2 mol%), MeOH, -75°	 (94), >99	59
	HCN (2.0 eq), catalyst 7 (10 mol%), toluene, -20°, 20 h	 (88), 81	37
	TMSCN (2.0 eq), phenol (20 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH2Cl2, -40°, 44 h	 (92), 95	26, 27
	TMSCN (4 eq), <i>t</i> -BuOH (1.1 eq), polymer-supported catalyst 8 (10 mol%), CH2Cl2, -50°, 59 h	 1 (98), 85	73

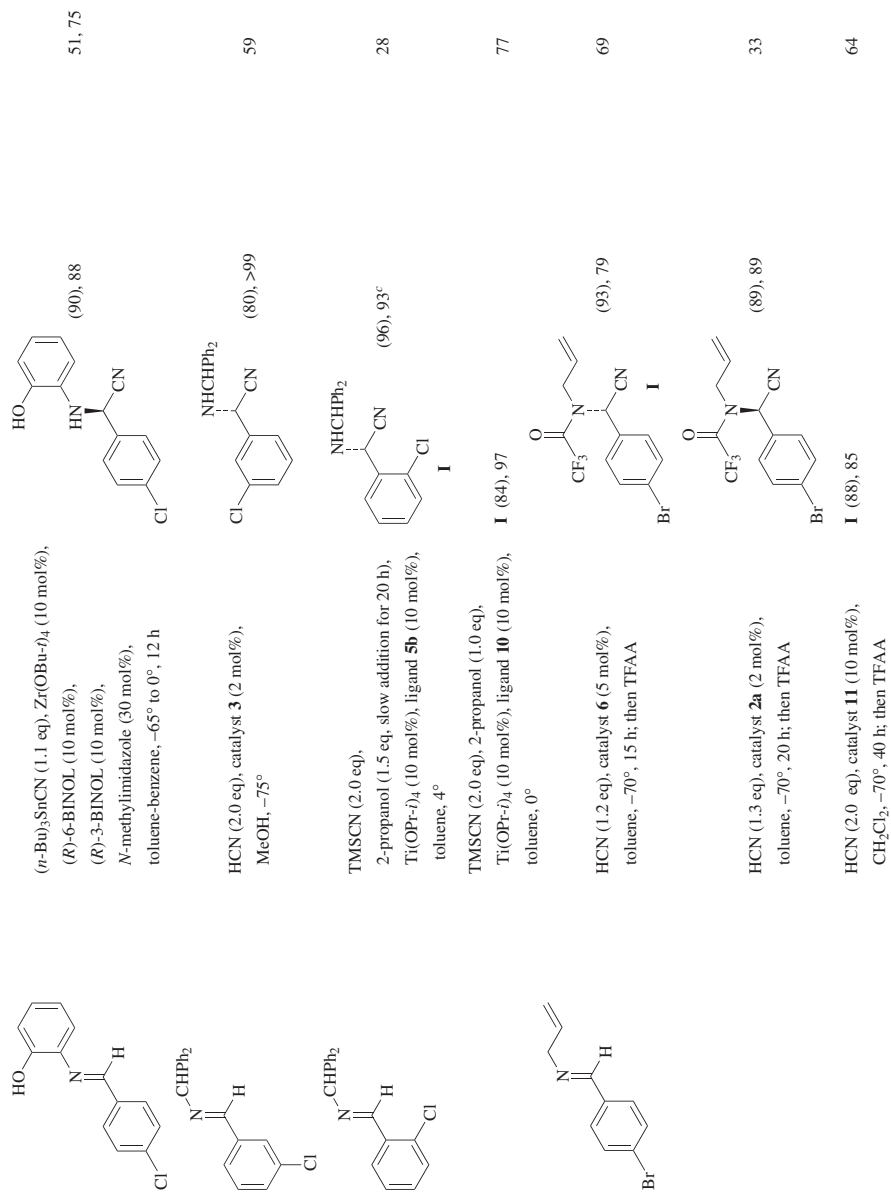
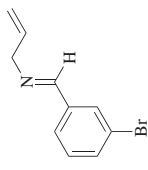
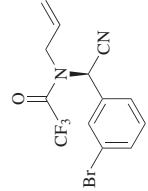
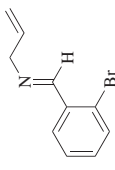
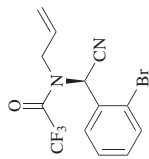
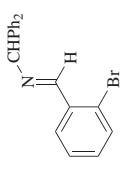
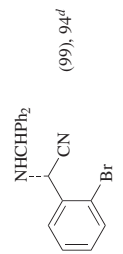
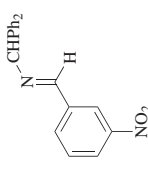
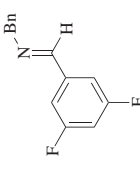
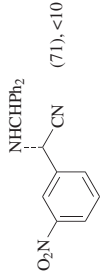
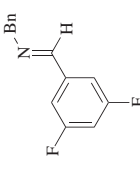
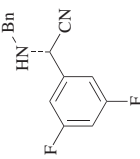


TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 20 h; then TFAA	 (87), 90	33
	HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 36 h; then TFAA	 (88), 95	33
	TMSCN (2.0 eq), 2-propanol (1.5 eq, slow addition for 20 h), Ti(OPr- <i>i</i>) ₄ (10 mol%), ligand 5b (10 mol%), toluene, 4°	 (99), 94 ^d	28
	TMSCN (2.0 eq), 2-propanol (1.0 eq), Ti(OPr- <i>i</i>) ₄ (10 mol%), ligand 10 (10 mol%), toluene, 0°	1 (80), >98	77
	HCN (2.0 eq), catalyst 3 (2 mol%), MeOH, -75°	 (71), <10	59
	HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°	 (59), 98	67

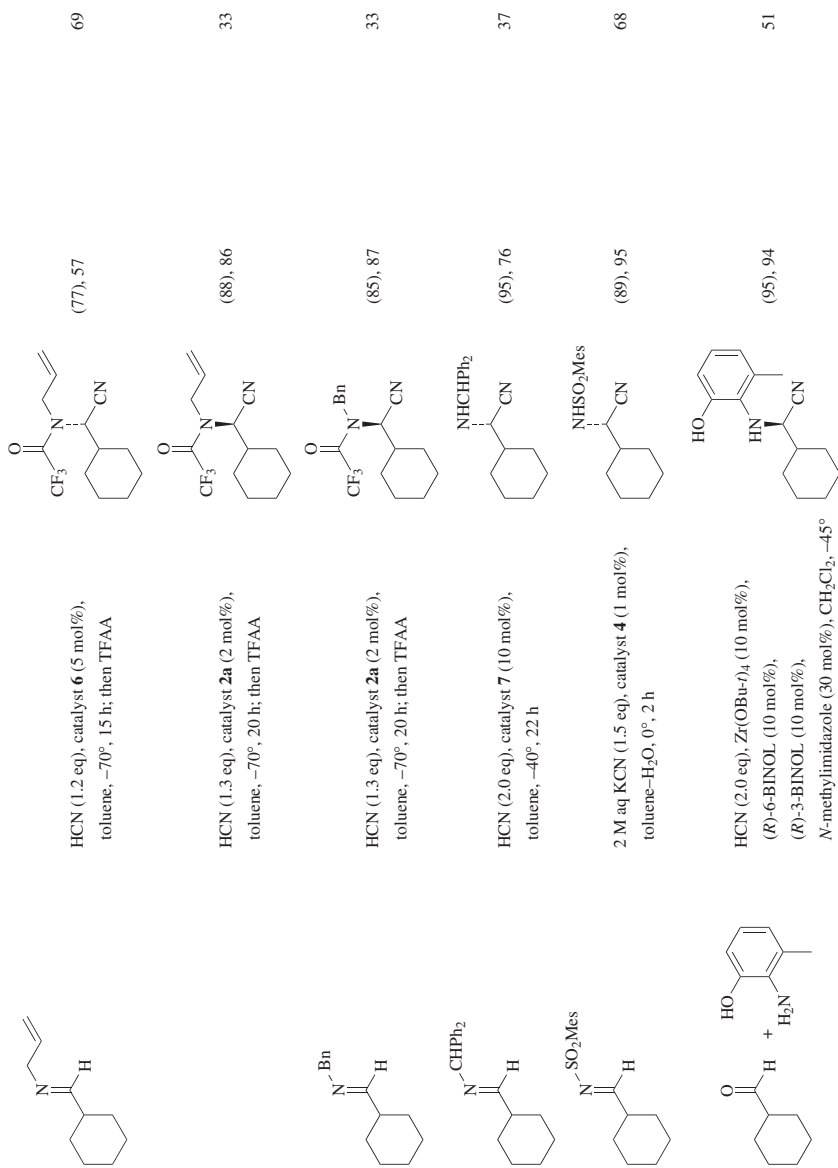
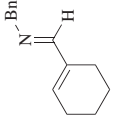
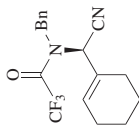
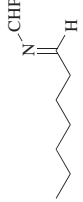

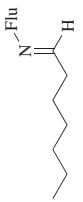
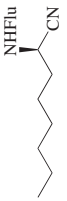
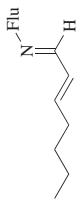

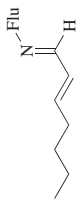

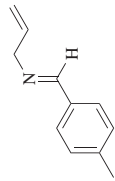
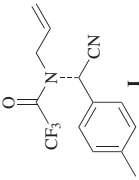


TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70° , 20 h; then TFAA	 (90), 91	33
	HCN (2.0 eq), catalyst 7 (10 mol%), toluene, -40° , 22 h	 (95), 63	37
	TMSCN (2.0 eq), catalyst 1 (9 mol%), CH_2Cl_2 , -40° , 24 h	 (80), 80	26, 27
	HCN (1.2 eq, slow addition for 24 h), TMSCN (20 mol%), catalyst 1 (9 mol%), CH_2Cl_2 , -40° , 36 h	 (75), 81	26, 27
	TMSCN (2.0 eq), phenol (50 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH_2Cl_2 , -40° , 24 h	 (66), 86	26, 27
	HCN (1.2 eq), catalyst 6 (5 mol%), toluene, -70° , 15 h; then TFAA	 (99), 94	69

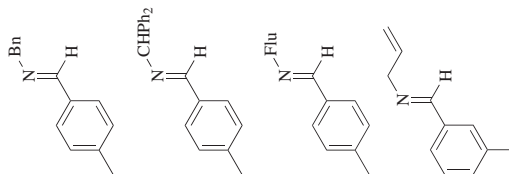
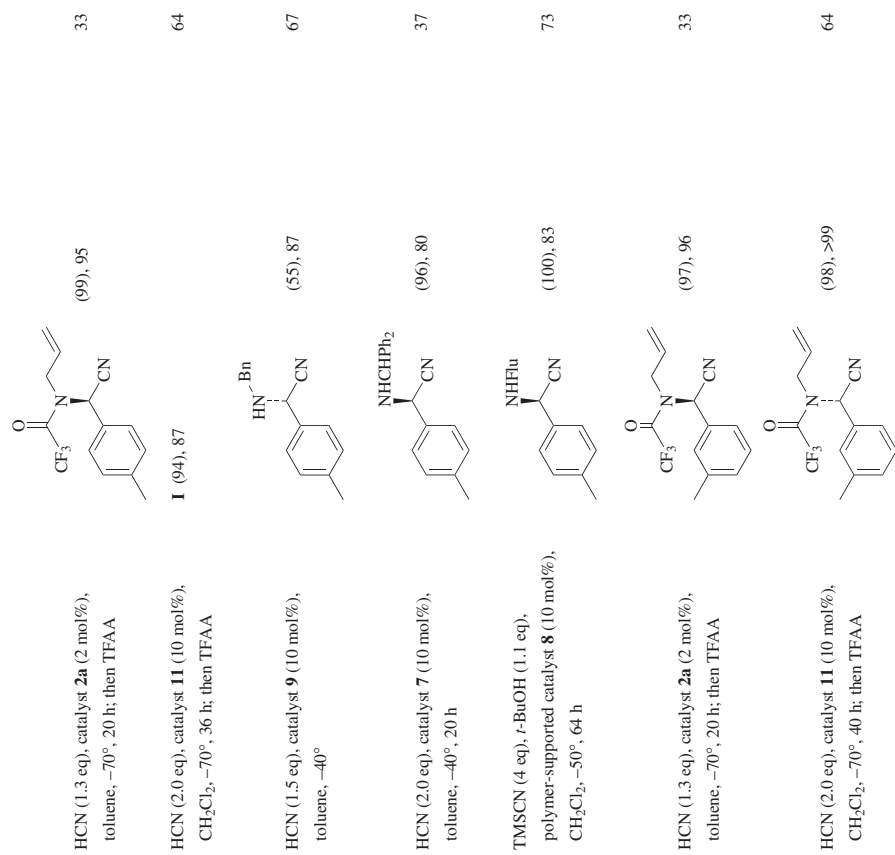


TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

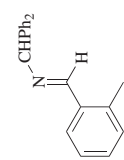
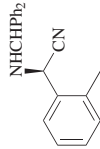
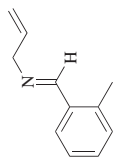
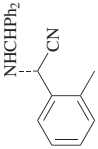
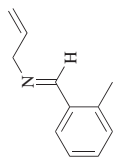
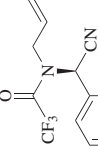
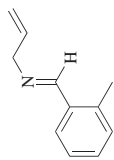
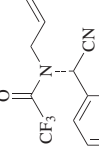
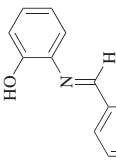
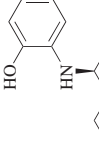
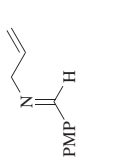
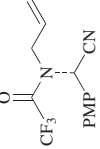
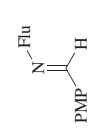
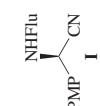
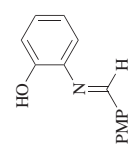
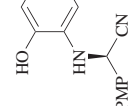
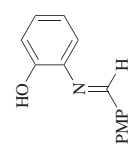
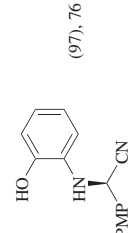
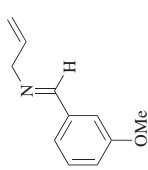
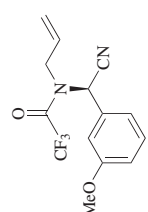
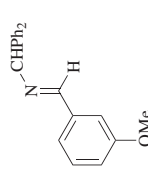
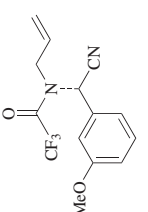
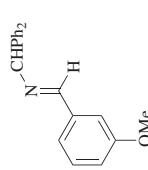
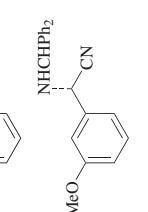
Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	HCN (2.0 eq), catalyst 7 (10 mol%), toluene, -40°, 12 h	 (88), 50	37
	TMSCN (2.0 eq), 2-propanol (1.0 eq), Ti(OPr- <i>i</i>) ₄ (10 mol%), ligand 10 (10 mol%), toluene, 0°	 (84), 98	77
	HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 20 h; then TFAA	 (96), 95	33
	HCN (2.0 eq), catalyst 11 (10 mol%), CH ₂ Cl ₂ , -70°, 40 h; then TFAA	 (86), 89	64
	(<i>n</i> -Bu) ₃ SnCN (1.1 eq), Zr(OBu- <i>t</i>) ₄ (10 mol%), (<i>R</i>)-6-BINOL (10 mol%), (<i>R</i>)-3-BINOL (10 mol%), <i>N</i> -methylimidazole (30 mol%), toluene-benzene, -65° to 0°, 12 h	 (96), 89	51, 75
	HCN (1.2 eq), catalyst 6 (5 mol%), toluene, -70°, 15 h; then TFAA	 (93), 91	69

TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 <chem>C=C(Nc1ccc2c(c1)C=CC2)c3ccccc3</chem>	TMSCN (2.0 eq), phenol (20 mol%, slow addition for 17 h), catalyst 1 (9 mol%), CH ₂ Cl ₂ , -40°, 44 h	 (93), 93	26, 27
 <chem>C=C(Nc1ccc(O)c1)c2ccccc2</chem>	TMSCN (4 eq), <i>t</i> -BuOH (1.1 eq), polymer-supported catalyst 8 (10 mol%), CH ₂ Cl ₂ , -50°, 41 h	 1 (98), 83	73
 <chem>C=C(Nc1ccc(O)c1)c2ccccc2</chem>	(<i>n</i> -Bu) ₃ SnCN (1.1 eq), Zr(OBu- <i>t</i>) ₄ (10 mol%), (<i>R</i>)-6-BINOL (10 mol%), (<i>R</i>)-3-BINOL (10 mol%), <i>N</i> -methylimidazole (30 mol%), toluene-benzene, -65° to 0°, 12 h	 (97), 76	51, 75
 <chem>C=C(Nc1ccc(OC)cc1)c2ccccc2</chem>	HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 20 h; then TFAA	 (99), 93	33
 <chem>C=C(Nc1ccc(OC)cc1)c2ccccc2</chem>	HCN (2.0 eq), catalyst 11 (10 mol%), CH ₂ Cl ₂ , -70°, 40 h; then TFAA	 (96), >99	64
 <chem>C=C(Nc1ccc(OC)cc1)c2ccccc2</chem>	HCN (2.0 eq), catalyst 3 (2 mol%), MeOH, -75°	 (82), 80	59

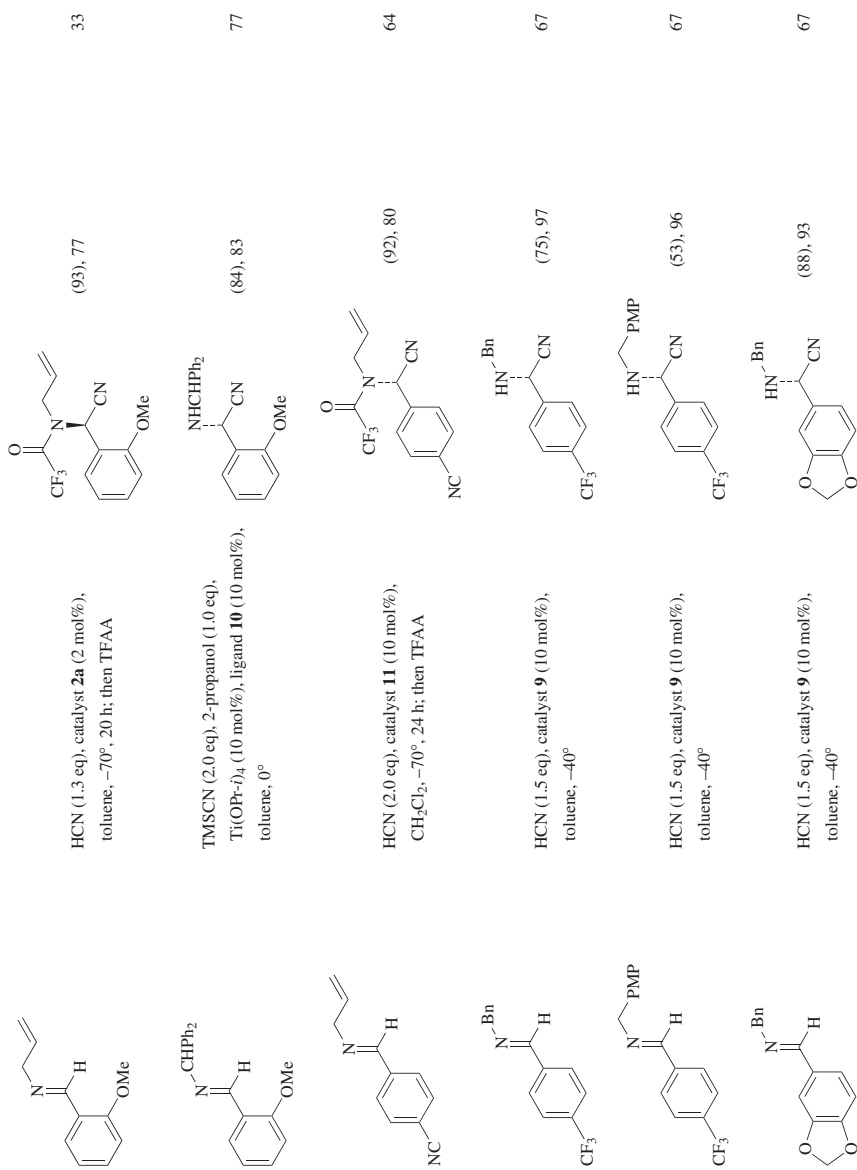
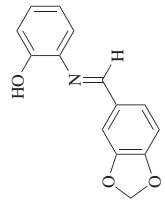
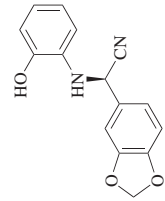
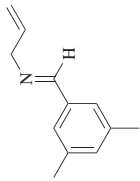
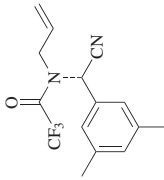
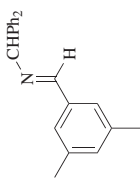
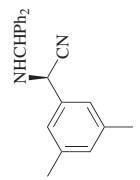
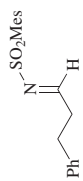
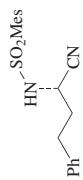
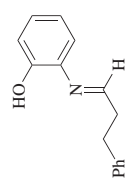
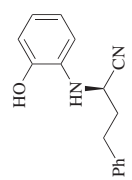


TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C ₈	<p>(<i>n</i>-Bu)₃SnCN (1.1 eq), Zr(OBu-<i>t</i>)₄ (10 mol%), <i>(R)</i>-6-BINOL (10 mol%), <i>(R)</i>-3-BINOL (10 mol%), <i>N</i>-methylimidazole (30 mol%), toluene-benzene, -65° to 0°, 12 h</p>	 (89), 80	51, 75
 C ₉	<p>HCN (2.0 eq), catalyst II (10 mol%), CH₂Cl₂, -70°, 48 h; then TFAA</p>	 (88), 90	64
 C ₉	<p>HCN (2.0 eq), catalyst 7 (10 mol%), toluene, -40°, 16 h</p>	 (96), 79	37
 C ₉	<p>2 M aq KCN (1.5 eq), catalyst 4 (1 mol%), toluene-H₂O, 0°, 2 h</p>	 (81), 90	68
 C ₉	<p>(<i>n</i>-Bu)₃SnCN (1.1 eq), Zr(OBu-<i>t</i>)₄ (10 mol%), <i>(R)</i>-6-BINOL (10 mol%), <i>(R)</i>-3-BINOL (10 mol%), <i>N</i>-methylimidazole (30 mol%), toluene-benzene, -65° to 0°, 12 h</p>	 (55), 83	51, 75

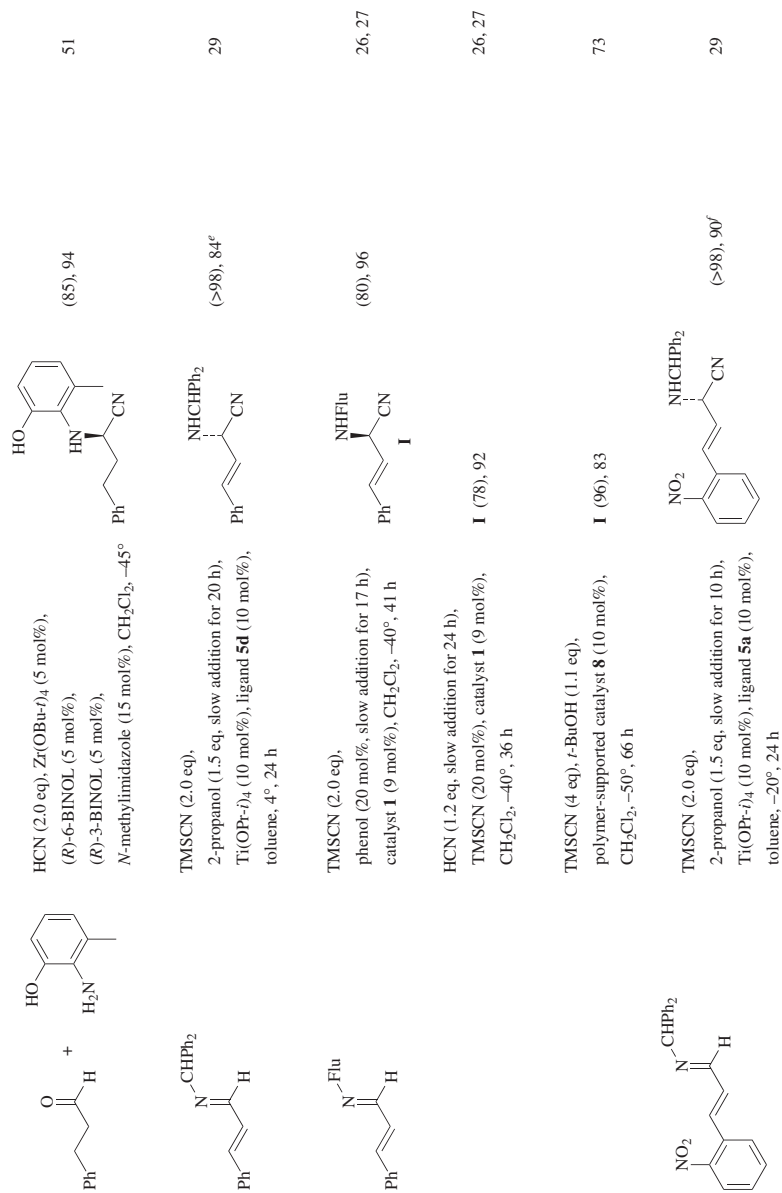
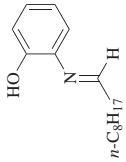
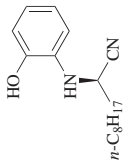
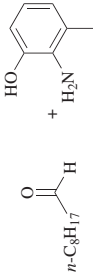
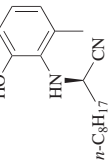
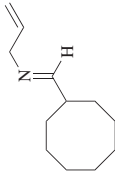
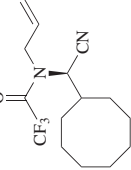
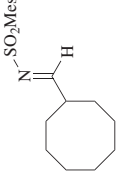
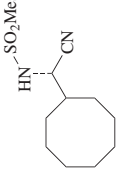
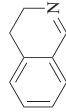
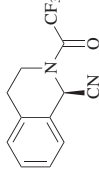


TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 $n\text{-C}_8\text{H}_{17}$	<p>(<i>n</i>-Bu)₃SnCN (1.1 eq), Zr(OBu-<i>t</i>)₄ (10 mol%), (<i>R</i>)-6-BINOL (10 mol%), (<i>R</i>)-3-BINOL (10 mol%), <i>N</i>-methylimidazole (30 mol%), toluene-benzene, -65° to 0°, 12 h</p>	 $n\text{-C}_8\text{H}_{17}$	51, 75 (72), 74
 $n\text{-C}_8\text{H}_{17}$	<p>HCN (2.0 eq), Zr(OBu-<i>t</i>)₄ (2 mol%), (<i>R</i>)-6-BINOL (2 mol%), (<i>R</i>)-3-BINOL (2 mol%), <i>N</i>-methylimidazole (6 mol%), CH₂Cl₂, -45°</p>	 $n\text{-C}_8\text{H}_{17}$	(86), 84 51
	<p>HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 20 h; then TFAA</p>		(65), 90 33
	<p>2 M aq KCN (1.5 eq), catalyst 4 (1 mol%), toluene-H₂O, 0°, 2 h</p>		(88), 97 68
	<p>HCN (1.3 eq), catalyst 2a (2 mol%), toluene, -70°, 20 h; then TFAA</p>		(88), 91 33

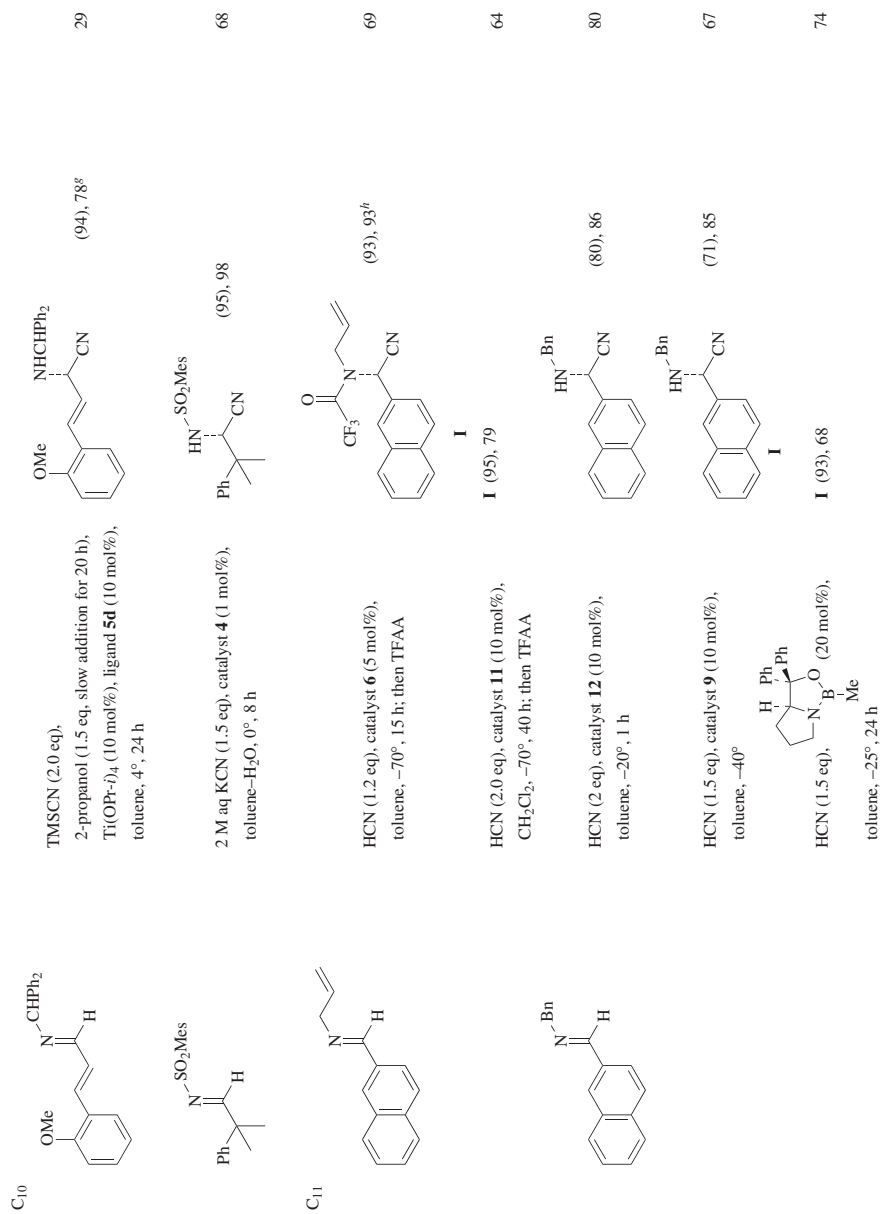
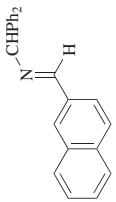
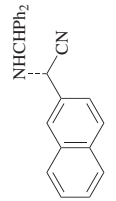
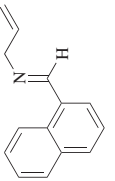
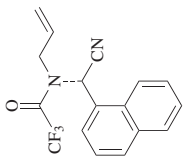
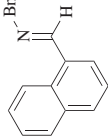
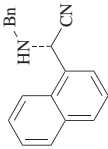
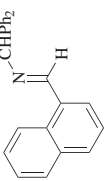
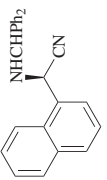

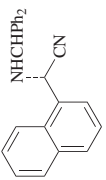

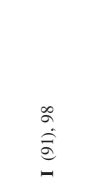


TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C ₁₁	<p>TMSCN (2.0 eq), 2-propanol (1.5 eq, slow addition for 20 h), Ti(OPr-<i>i</i>)₄ (10 mol%), ligand 5c (10 mol%), toluene, 4°</p>	 (100), 93 ⁱ	28
	<p>HCN (1.2 eq), catalyst 6 (5 mol%), toluene, -70°, 15 h; then TFAA</p>	 (95), 93	69
	<p>HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°</p>	 (85), 99	67
	<p>HCN (2.0 eq), catalyst 7 (10 mol%), toluene, -20°, 12 h</p>	 (90), 76	37
	<p>TMSCN (2.0 eq), 2-propanol (1.5 eq, slow addition for 20 h), Ti(OPr-<i>i</i>)₄ (10 mol%), ligand 5c (10 mol%), toluene, 4°</p>	 (93), 90 ⁱ	28
	<p>TMSCN (2.0 eq), 2-propanol (1.0 eq), Ti(OPr-<i>i</i>)₄ (10 mol%), ligand 10 (10 mol%), toluene, 0°</p>	 1 (91), 98	77

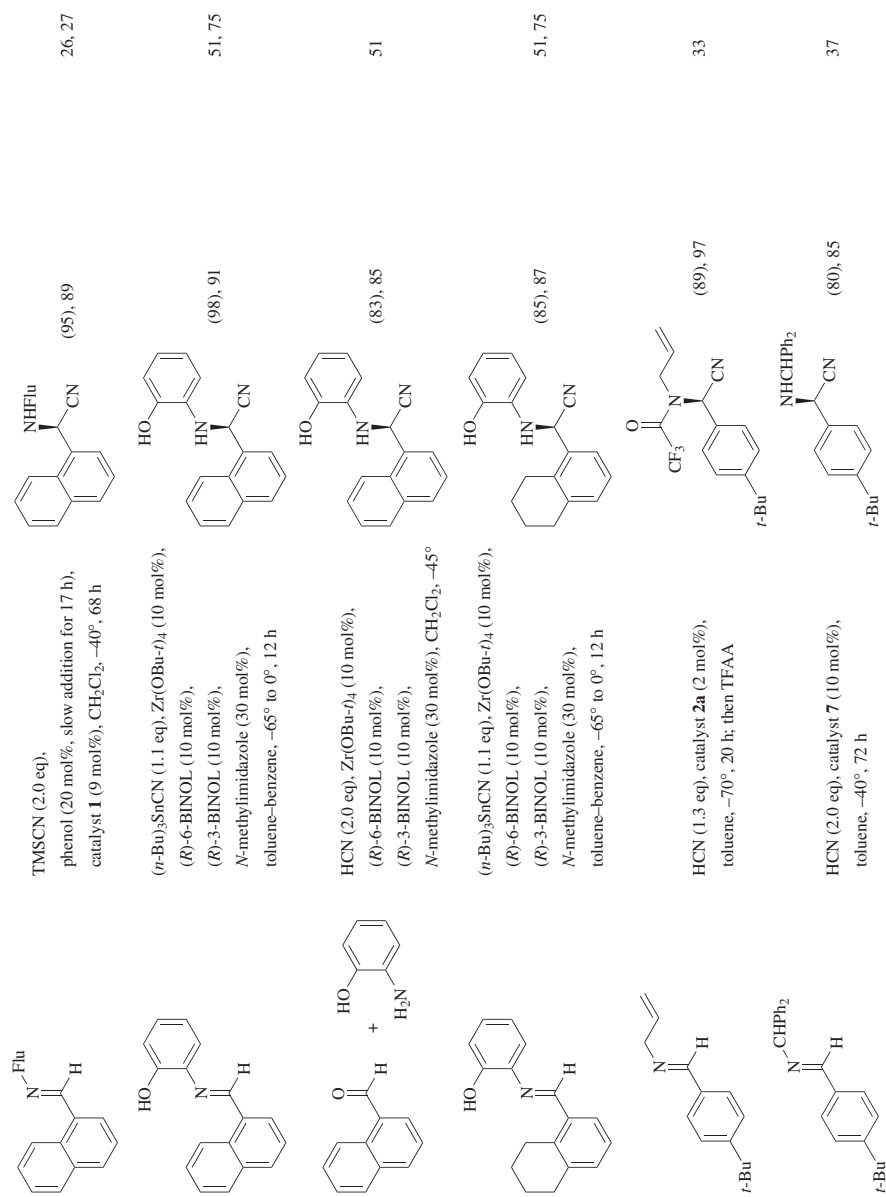
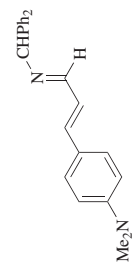
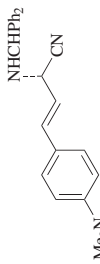
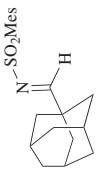
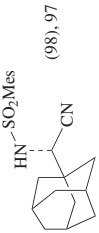
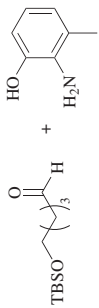
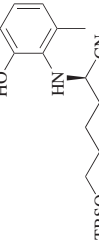
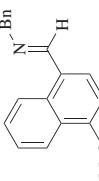
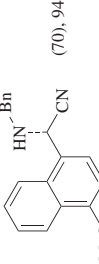
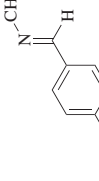
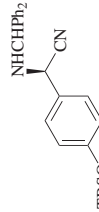
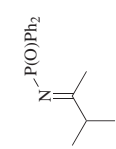
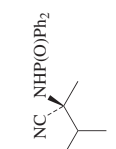
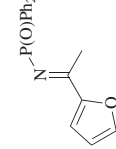
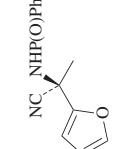
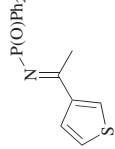
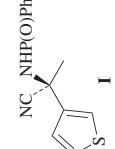
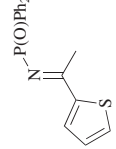
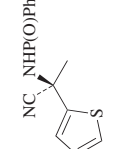
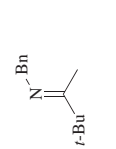
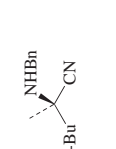




TABLE I. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES (Continued)

Aldimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 Me_2N	<p>TMSCN (2.0 eq), <i>n</i>-BuOH (1.5 eq, slow addition for 10 h), Ti(OPr-<i>t</i>)₄ (15 mol%), ligand 5a (15 mol%), toluene, -20°, 24 h</p>	 (93), 76	29
 $\text{N-SO}_2\text{Mes}$	<p>2 M aq KCN (1.5 eq), catalyst 4 (1 mol%), toluene-H₂O, 0°, 8 h</p>	 (98), 97	68
 TBSO	<p>H₂N</p>	 (80), 91	51
 N-Bn	<p>HCN (2.0 eq), Zr(OBu-<i>t</i>)₄ (5 mol%), (<i>R</i>)-6-BINOL (5 mol%), (<i>R</i>)-3-BINOL (5 mol%), <i>N</i>-methylimidazole (15 mol%), CH₂Cl₂, -45°</p>	 (70), 94	67
 TBSO	<p>HCN (1.5 eq), catalyst 9 (10 mol%), toluene, -40°</p>	 (98), 88	37

- a* After recrystallization, the product yield was 97%, 85% ee.
b After recrystallization, the product yield was 82%, >99% ee.
c After recrystallization, the product yield was 85%, >99% ee.
d After recrystallization, the product yield was 93%, >99% ee.
e After recrystallization, the product yield was 80%, 97% ee.
f After recrystallization, the product yield was 87%, 97% ee.
g After recrystallization, the product yield was 61%, 97% ee.
h After recrystallization from hexanes, the product yield was 55%, >99% ee.
i After recrystallization, the product yield was 80%, >99% ee.
j After recrystallization, the product yield was 87%, >99% ee.

TABLE 2. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF KETIMINES

Ketimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C ₅	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OP <i>i</i> -Pr) ₃ (2.5 mol%), ligand 13 (5 mol%), CH ₃ CH ₂ CN, -40°, 2.5 h	 (91), 80	40
 C ₆	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OP <i>i</i> -Pr) ₃ (2.5 mol%), ligand 13 (5 mol%), CH ₃ CH ₂ CN, -40°, 6 h	 (98), 98	40
 I	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OP <i>i</i> -Pr) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 21 h	 (93), 93	40
 I	HCN (1.5 eq), TMSCN (5 mol%), Gd(OP <i>i</i> -Pr) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 3 h	 (99), 99	41
 I	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OP <i>i</i> -Pr) ₃ (2.5 mol%), ligand 13 (5 mol%), CH ₃ CH ₂ CN, -40°, 10 h	 (94), 96	40
 I	HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°, 15 h	 (98), 70	38

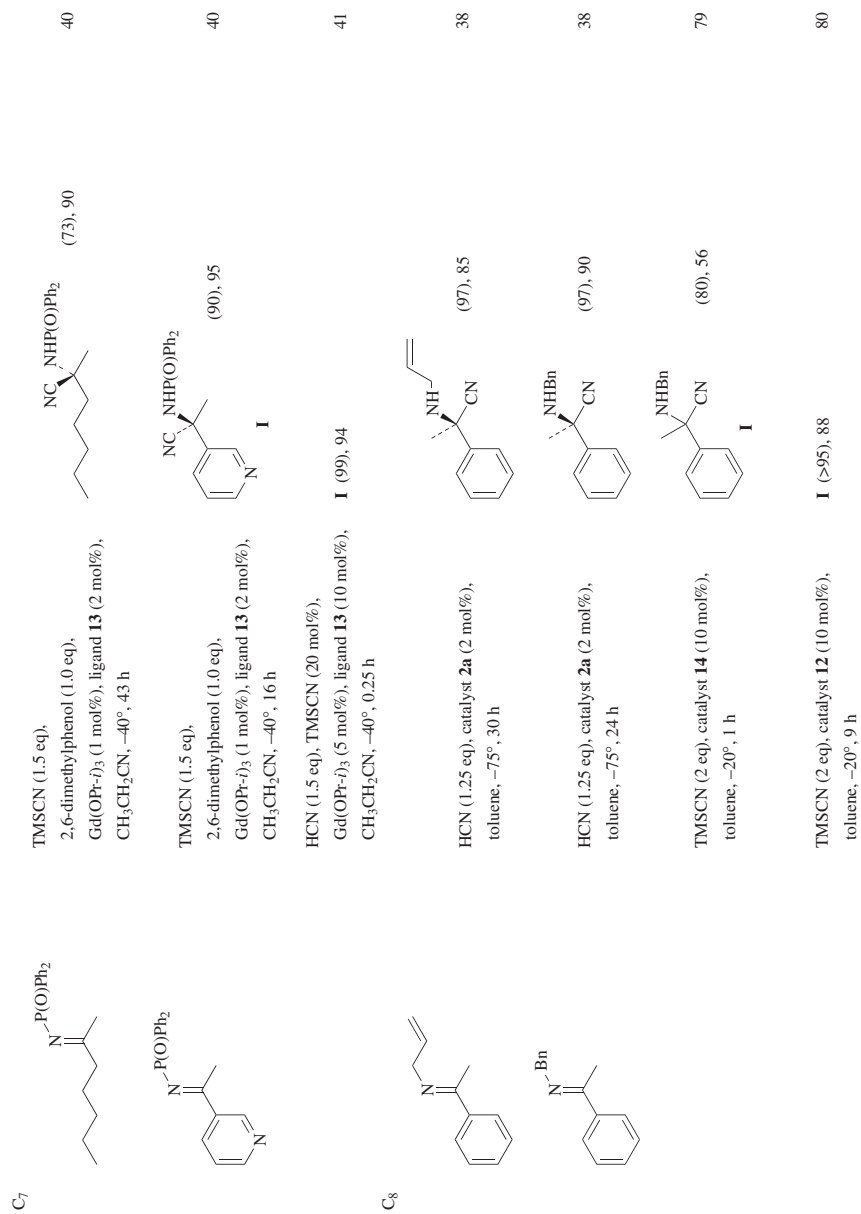
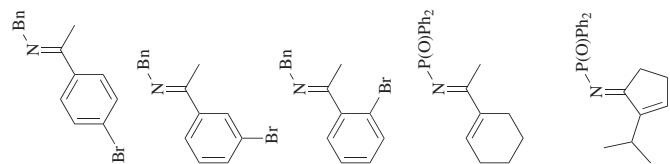
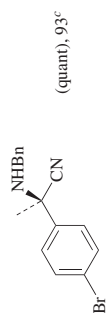


TABLE 2. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF KETIMINES (Continued)

C ₈	Ketimine	Conditions	Product(s) and Yield(s) (%), % ee		Refs.
			R	Time	
		HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°	OMe CF ₃ <i>t</i> -Bu Br	36 h (97), 93 50 h (95), 92 30 h (95), 89 40 h (95), 92 ^a	38
		TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OPr- <i>i</i>) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 30 h	(94), 92		40
		HCN (1.5 eq), TMSCN (5 mol%), Gd(OPr- <i>i</i>) ₃ (0.1 mol%), ligand 13 (0.2 mol%), CH ₃ CH ₂ CN, -40°, 19 h	I (97), 90		41
		HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°, 80 h	(quant), 93 ^b		38
		TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OPr- <i>i</i>) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 13 h	I (99), 93	(93), 95	40
		HCN (1.5 eq), TMSCN (2.5 mol%), Gd(OPr- <i>i</i>) ₃ (0.1 mol%), ligand 13 (0.2 mol%), CH ₃ CH ₂ CN, -40°, 54 h	I (99), 93		41

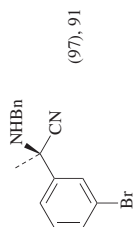


HCN (1.25 eq), catalyst **2a** (2 mol%),
toluene, -75° , 80 h



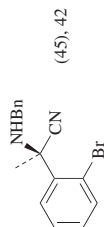
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HCN (1.25 eq), catalyst **2a** (2 mol%),
toluene, -75° , 60 h



38

HCN (1.25 eq), catalyst **2a** (2 mol%),
toluene, -75° , 90 h



38

TMSCN (1.5 eq),
2,6-dimethylphenol (1.0 eq),
Gd(OPr-*t*)₃ (1 mol%), ligand **13** (2 mol%),
CH₃CH₂CN, -40° , 52 h



40

TMSCN (1.5 eq),
2,6-dimethylphenol (1.0 eq),
Gd(OPr-*t*)₃ (5 mol%), ligand **13** (10 mol%),
CH₃CH₂CN, -40° , 3 days



86

TMSCN (2.0 eq),
2,6-dimethylphenol (1.0 eq),
Gd(HMDS)₃ (2.5 mol%),
ligand **13** (3.75 mol%),
CH₃CH₂CN, -40° , 2 days

I (99), 98

86

TABLE 2. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF KETIMINES (Continued)

Ketimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°, 80 h	 (98), 91	38
	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OPr- <i>i</i>) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 38 h	 (89), 87	40
	HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°, 60 h	 (98), 88	38
	HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°, 65 h	 (quant), 95 ^a	38
	HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°, 17 h	 (96), 69	38
	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OPr- <i>i</i>) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 31 h	 (97), 95	40

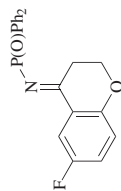


TMSCN (1.5 eq),
2,6-dimethylphenol (1.0 eq),
Gd(OP*i*-t)₃ (2.5 mol%), ligand **13** (5 mol%),
CH₃CH₂CN, -40°, 8 h

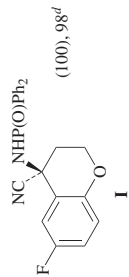


40

(94), 88



TMSCN (1.1 eq),
2,6-dimethylphenol (1.0 eq),
Gd(OP*i*-t)₃ (1 mol%), ligand **13** (2 mol%),
CH₃CH₂CN, -40°, 83 h



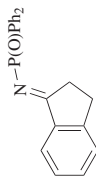
40

(100), 98^d

HCN (1.5 eq), TMSCN (5 mol%),
Gd(OP*i*-t)₃ (0.5 mol%),
ligand **13** (1 mol%),
CH₃CH₂CN, -40°, 1.3 h

1 (96), 93

41



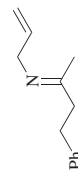
TMSCN (1.5 eq),
2,6-dimethylphenol (1.0 eq),
Gd(OP*i*-t)₃ (2.5 mol%), ligand **13** (5 mol%),
CH₃CH₂CN, -40°, 48 h



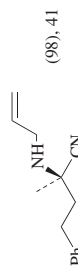
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(98), 97

C₁₀

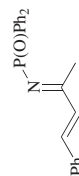


HCN (1.25 eq), catalyst **2a** (2 mol%),
toluene, -75°, 17 h



38

(98), 41

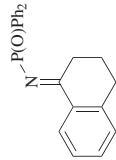
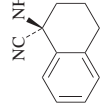
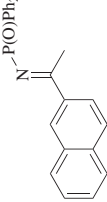
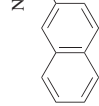
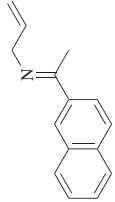
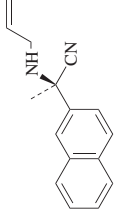
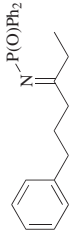
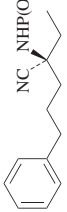


TMSCN (1.5 eq),
2,6-dimethylphenol (1.0 eq),
Gd(OP*i*-t)₃ (1 mol%), ligand **13** (2 mol%),
CH₃CH₂CN, -40°, 38 h

(93), 96

40

TABLE 2. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF KETIMINES (Continued)

Ketimine	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C ₁₀	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OPr- <i>i</i>) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 22 h	 (92), 92	40
 C ₁₂	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OPr- <i>i</i>) ₃ (1 mol%), ligand 13 (2 mol%), CH ₃ CH ₂ CN, -40°, 67 h	 (99), 86	40
	HCN (1.25 eq), catalyst 2a (2 mol%), toluene, -75°, 65 h	 (97), 89	38
	TMSCN (1.5 eq), 2,6-dimethylphenol (1.0 eq), Gd(OPr- <i>i</i>) ₃ (2.5 mol%), ligand 13 (5 mol%), CH ₃ CH ₂ CN, -40°, 16 h	 (73), 53	40

^a After recrystallization from hexanes, the product yield was 75%, >99.9% ee.

^b After recrystallization from hexanes, the product yield was 79%, >99.9% ee.

^c After recrystallization from hexanes, the product yield was 76%, >99.9% ee.

^d After recrystallization from CHCl₃-hexane, the product yield was 93%, >99% ee.

TABLE 3. CATALYTIC ENANTIOSELECTIVE REISSERT REACTIONS

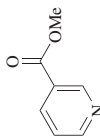
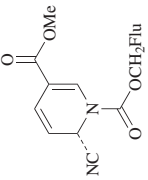
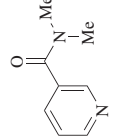
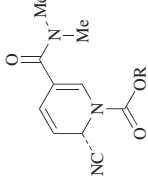
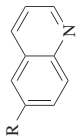
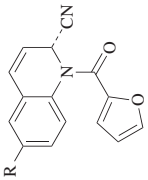
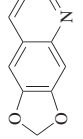
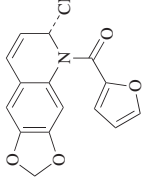
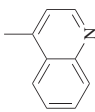
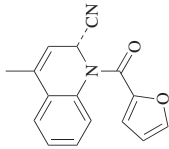
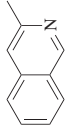
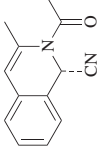
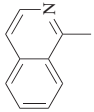
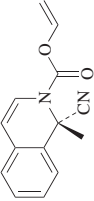
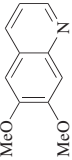
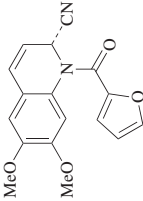
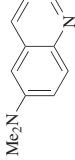
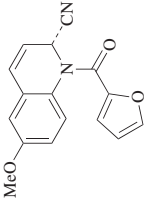
Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	TMSCN (2.0 eq), Et ₂ AlCl (5 mol%), ligand 15 (10 mol%), FmocCl (1.4 eq), CH ₂ Cl ₂ , -60°, 5 h	 (85), 57 ^a	50
	TMSCN (2.0 eq), Et ₂ AlCl (5 mol%), ligand 15 (10 mol%), ROCOCl (1.4 eq), CH ₂ Cl ₂ , -60°, 5 h	 R Me (98), 91 Fm (89), 93	50
	TMSCN (x eq), catalyst 16a (9 mol%), 2-furoyl chloride (x eq), -40°	 (91), 85 (57), 67 (63), 67 (74), 89	47, 48
	1. TMSCN (2.0 eq), slow addition for 12 h 2. Catalyst 16a (9 mol%), 2-furoyl chloride (2.0 eq), CH ₂ Cl ₂ -toluene, -40°, 64 h	 (77), 83	47, 48

TABLE 3. CATALYTIC ENANTIOSELECTIVE REISSERT REACTIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C ₁₀	TMSCN (2.0 eq), catalyst 16a (9 mol%), 2-furoyl chloride (2.0 eq), CH ₂ Cl ₂ -toluene, -40°, 40 h	 (71), 54	48
	TMSCN (2.0 eq), catalyst 16a (9 mol%), acetyl chloride (1.1 eq), CH ₂ Cl ₂ , -78°, 24 h	 (73), 75	47, 48
	TMSCN (2.0 eq), catalyst 17 (2.5 mol%), vinyl chloroformate (1.8 eq), CH ₂ Cl ₂ , -60°, 48 h	 (88), 89	49
 C ₁₁	1. TMSCN (2.0 eq), slow addition for 12 h 2. Catalyst 16a (9 mol%), 2-furoyl chloride (2.0 eq), CH ₂ Cl ₂ -toluene, -40°, 40 h	 (99), 91	47, 48
	1. TMSCN (2.0 eq), slow addition for 12 h 2. Catalyst 16a (9 mol%), 2-furoyl chloride (2.0 eq), CH ₂ Cl ₂ -toluene, -40°, 40 h	 (72), 89	47, 48

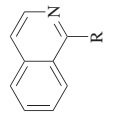
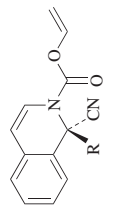
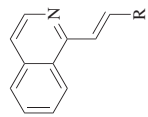
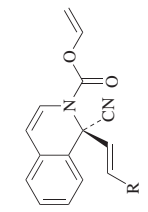
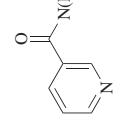
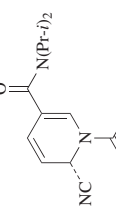
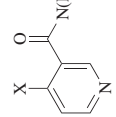
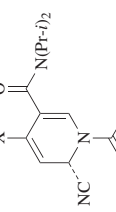
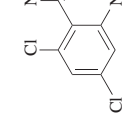
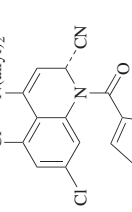
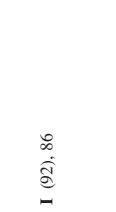
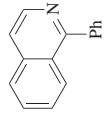
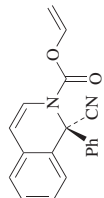
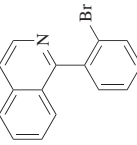
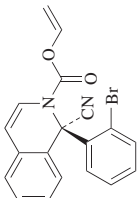
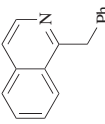
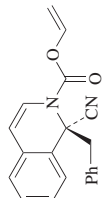
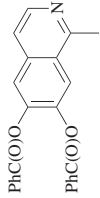
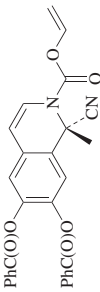
 C ₁₁₋₁₂	<p>TMSCN (2.0 eq), catalyst 17 (2.5 mol%), vinyl chloroformate (1.8 eq), CH₂Cl₂, -60°, 48 h</p>		<table border="0"> <tr> <td>R</td> <td></td> </tr> <tr> <td>Et</td> <td>(98), 88</td> </tr> <tr> <td>CH₂OMe</td> <td>(84), 73</td> </tr> </table>	R		Et	(98), 88	CH ₂ OMe	(84), 73	49
R										
Et	(98), 88									
CH ₂ OMe	(84), 73									
 C ₁₂	<p>TMSCN (2.0 eq), catalyst 17 (2.5 mol%), vinyl chloroformate (1.8 eq), CH₂Cl₂, -60°, 48 h</p>		<table border="0"> <tr> <td>R</td> <td></td> </tr> <tr> <td>H</td> <td>(80), 84</td> </tr> <tr> <td>Me</td> <td>(88), 87</td> </tr> </table>	R		H	(80), 84	Me	(88), 87	49
R										
H	(80), 84									
Me	(88), 87									
 C ₁₂	<p>TMSCN (2.0 eq), Et₂AlCl (5 mol%), ligand 15 (10 mol%), ROCOCl (1.4 eq), CH₂Cl₂, -60°, 5 h</p>		<table border="0"> <tr> <td>R</td> <td></td> </tr> <tr> <td>neopentyl</td> <td>(98), 93</td> </tr> <tr> <td>Fm</td> <td>(98), 96</td> </tr> </table>	R		neopentyl	(98), 93	Fm	(98), 96	50
R										
neopentyl	(98), 93									
Fm	(98), 96									
 C ₁₅	<p>TMSCN (2.0 eq), Et₂AlCl (10 mol%), ligand 18 (10 mol%), neopentyl-OCOC1 (1.4 eq), CH₂Cl₂, -60°, 27 h</p>		<table border="0"> <tr> <td>X</td> <td>Time</td> </tr> <tr> <td>Cl</td> <td>27 h (92), 91</td> </tr> <tr> <td>Br</td> <td>36 h (89), 86</td> </tr> </table>	X	Time	Cl	27 h (92), 91	Br	36 h (89), 86	50
X	Time									
Cl	27 h (92), 91									
Br	36 h (89), 86									
 C ₁₅	<p>TMSCN (2.0 eq), catalyst 16a (1 mol%), 2-furyl chloride (2.0 eq), CH₂Cl₂, -40°, 40 h</p>		<table border="0"> <tr> <td>R</td> <td></td> </tr> <tr> <td></td> <td>(91), 93</td> </tr> </table>	R			(91), 93	48		
R										
	(91), 93									
	<p>TMSCN (4.0 eq), polymer-supported catalyst 16b (3 mol%), 2-furyl chloride (4.0 eq), CH₂Cl₂, -40°, 40 h</p>		<table border="0"> <tr> <td>I</td> <td>(92), 86</td> </tr> </table>	I	(92), 86	48				
I	(92), 86									

TABLE 3. CATALYTIC ENANTIOSELECTIVE REISSERT REACTIONS (Continued)

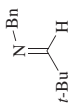
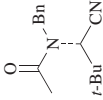
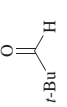
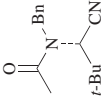
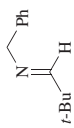
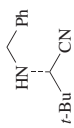
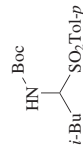
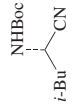
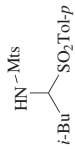

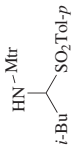
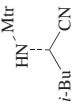
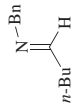
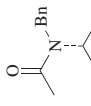
Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C_{15}	TMSCN (2.0 eq), catalyst 17 (1 mol%), vinyl chloroformate (1.8 eq), CH_2Cl_2 , -50° , 48 h	 (88), 95	49
 C_{16}	TMSCN (2.0 eq), catalyst 17 (1 mol%), vinyl chloroformate (1.8 eq), CH_2Cl_2 , -40° , 72 h	 (59), 93	49
 C_{16}	TMSCN (2.0 eq), catalyst 17 (2.5 mol%), vinyl chloroformate (1.8 eq), CH_2Cl_2 , -60° , 48 h	 (95), 92	49
 C_{24}	TMSCN (2.0 eq), catalyst 17 (2.5 mol%), vinyl chloroformate (1.8 eq), CH_2Cl_2 , -60° , 48 h	 (94), 94	49

^a After recrystallization, the product yield was 42%, >99% ee.

TABLE 4. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES: NOV. 2006 TO AUG. 2007

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 $\text{HN}^{\text{Boc}}-\text{C}(\text{SO}_2\text{Tol-}p)\text{=CH-CH}_3$	Acetone cyanohydrin (2 eq), K_2CO_3 (5.0 eq), catalyst 19 (10 mol%), toluene- H_2O , -20° , 42 h	 $\text{NHBoc}-\text{C}(\text{CN})-\text{CH}_2-\text{CH}_3$ (85), 78	186
 $\text{HN}^{\text{Boc}}-\text{C}(\text{SO}_2\text{Tol-}p)\text{=CH-CH}_2\text{CH}_3$	Acetone cyanohydrin (2 eq), K_2CO_3 (5.0 eq), catalyst 19 (10 mol%), toluene- H_2O , -20° , 42 h	 $\text{NHBoc}-\text{C}(\text{CN})-\text{CH}_2\text{CH}_2\text{CH}_3$ (88), 80	186
 $\text{HN}^{\text{Boc}}-\text{C}(\text{SO}_2\text{Tol-}p)\text{=CH-CH}_2\text{CH}_3$	Acetone cyanohydrin (2 eq), K_2CO_3 (5.0 eq), catalyst 19 (10 mol%), toluene- H_2O , -20° , 42 h	 $\text{NHBoc}-\text{C}(\text{CN})-\text{CH}_2\text{CH}_2\text{CH}_3$ (92), 82	186
 $\text{HN}^{\text{Mts}}-\text{C}(\text{SO}_2\text{Tol-}p)\text{=CH-CH}_2\text{CH}_3$	KCN (1.05 eq), catalyst 4 (1 mol%), toluene- H_2O , 0° , 1.5 h	 $\text{HN}^{\text{Mts}}-\text{C}(\text{CN})-\text{CH}_2\text{CH}_2\text{CH}_3$ (99), 97	187
 $\text{N}^{\text{Bn}}\text{=C}(\text{H})-\text{C}(\text{SO}_2\text{Tol-}p)\text{=CH-CH}_3$	Acetyl cyanide (1.5 eq), catalyst <i>ent</i> - 2b (1 mol%), toluene, -40°	 $\text{N}^{\text{Bn}}\text{=C}(\text{CN})-\text{CH}_2\text{CH}_2\text{CH}_3$ (87), 95	188
 $\text{O}=\text{C}(\text{H})-\text{C}(\text{SO}_2\text{Tol-}p)\text{=CH-CH}_3$	Acetyl cyanide (1.5 eq), catalyst <i>ent</i> - 2b (5 mol%), toluene, -40° , 36 h	 I (92), 92	189
 $\text{HN}^{\text{Boc}}-\text{C}(\text{SO}_2\text{Tol-}p)\text{=CH-CH}_2\text{CH}_3$	Acetone cyanohydrin (2 eq), K_2CO_3 (5.0 eq), catalyst 19 (10 mol%), toluene- H_2O , -20° , 42 h	 $\text{NHBoc}-\text{C}(\text{CN})-\text{CH}_2\text{CH}_2\text{CH}_3$ (85), 88	186

TABLE 4. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES: NOV. 2006 TO AUG. 2007 (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	Acetyl cyanide (1.5 eq), catalyst ent-2b (1 mol%), toluene, -40°	 (62), 96	188
 + PhCH ₂ NH ₂	Acetyl cyanide (1.5 eq), catalyst ent-2b (1 mol%), toluene, -40°, 36 h	 (46), 94	189
	HCN (1.2 eq), catalyst 20 (10 mol%), toluene, -40°, 4 h	 (85), 16	192
	Acetone cyanohydrin (2 eq), K ₂ CO ₃ (5.0 eq), catalyst 19 (10 mol%), toluene-H ₂ O, -20°, 42 h	 (90), 68	186
	KCN (1.05 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 1 h	 (96), 91	187
	KCN (1.05 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 1 h	 (99), 93	187
	Acetyl cyanide (1.5 eq), catalyst ent-2b (1 mol%), toluene, -40°	 (76), 94	188

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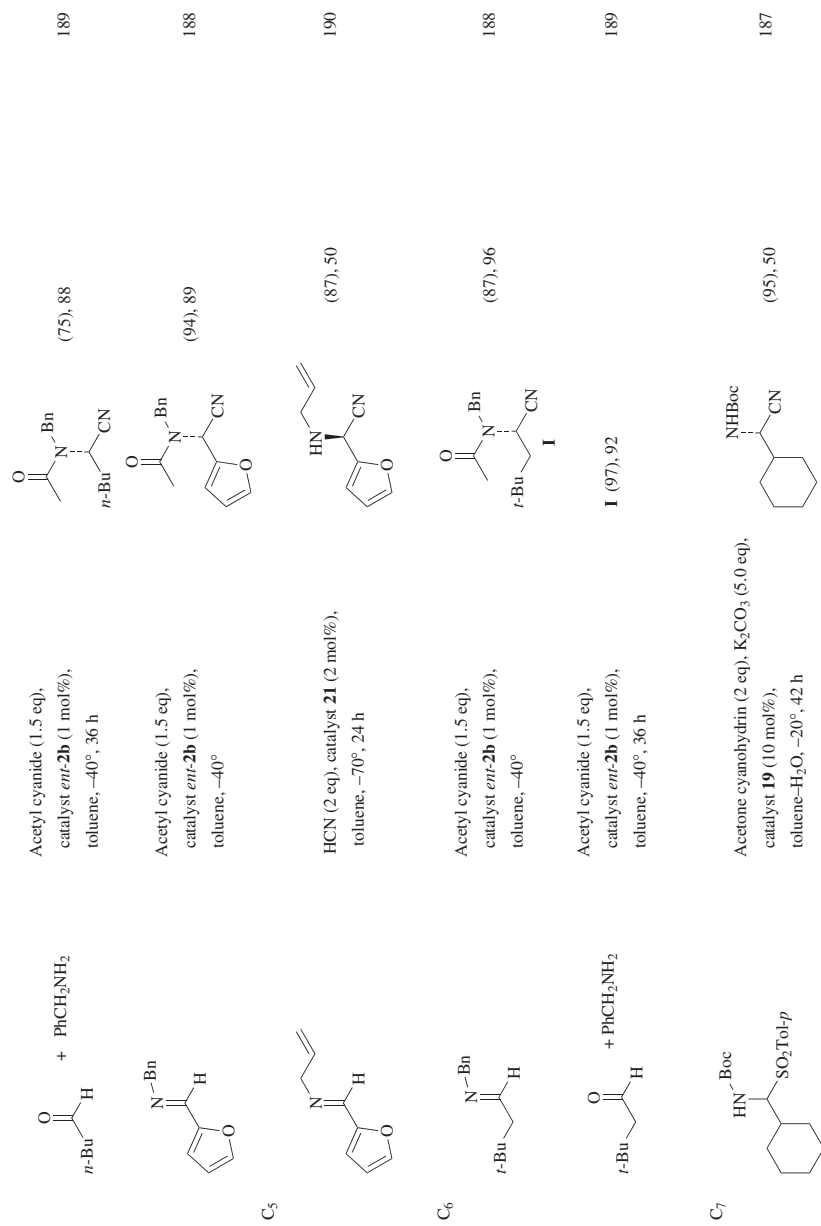
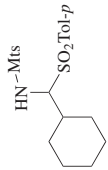
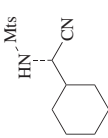
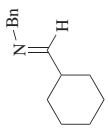
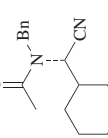
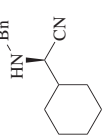
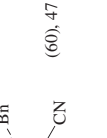
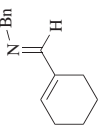
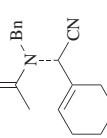
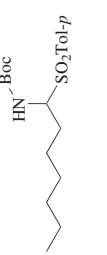
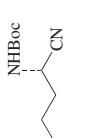
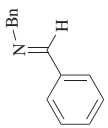
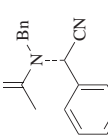


TABLE 4. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES: NOV. 2006 TO AUG. 2007 (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	KCN (1.05 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 1.5 h	 (99), 97	187
	Acetyl cyanide (1.5 eq), catalyst <i>ent-2b</i> (1 mol%), toluene, -40°	 (88), 92	188
	HCN (2 eq), catalyst 21 (2 mol%), toluene, -50°, 24 h	 (60), 47	190
	Acetyl cyanide (1.5 eq), catalyst <i>ent-2b</i> (1 mol%), toluene, -40°	 (82), 98	188
	Acetone cyanohydrin (2 eq), K ₂ CO ₃ (5.0 eq), catalyst 19 (10 mol%), toluene-H ₂ O, -20°, 42 h	 (95), 72	186
	Acetyl cyanide (1.5 eq), catalyst <i>ent-2b</i> (1 mol%), toluene, -40°	 (94), 96	188

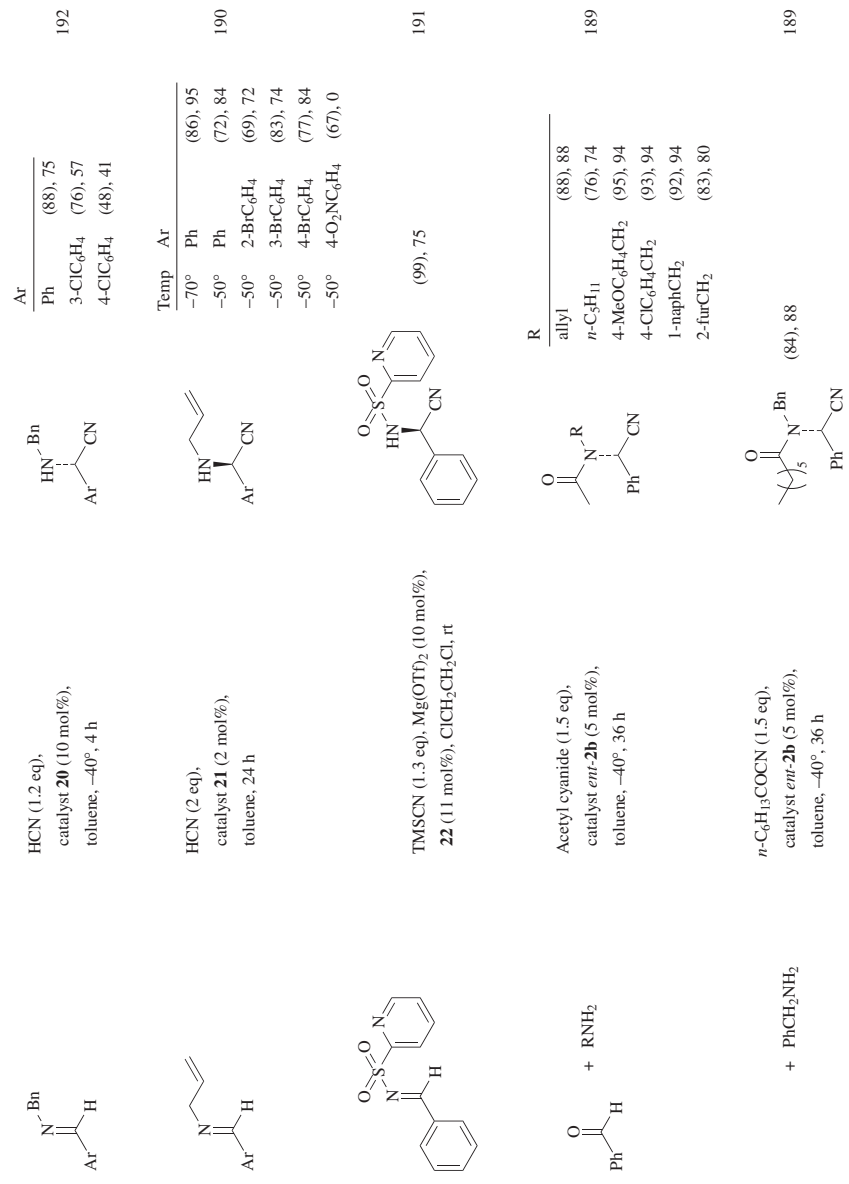
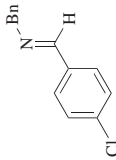
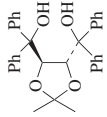
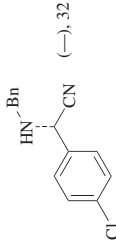
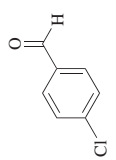
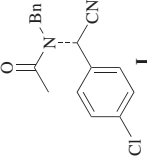
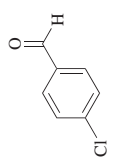
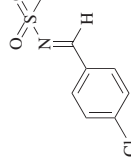
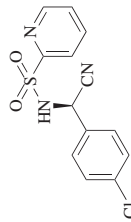
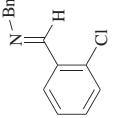
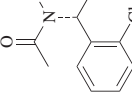


TABLE 4. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES: NOV. 2006 TO AUG. 2007 (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	<p>HCN (1.5 eq), TADDOL (10 mol%), toluene, -40°, 3 d</p> <p>TADDOL = </p>	 <p>(-), 32</p>	193
	<p>Acetyl cyanide (1.5 eq), catalyst <i>ent</i>-2b (1 mol%), toluene, -40°</p>	 <p>(87), 98</p>	188
	<p>Acetyl cyanide (1.5 eq), catalyst <i>ent</i>-2b (5 mol%), toluene, -40°, 36 h</p>	<p>I (78), 92</p>	189
	<p>TMSCN (1.3 eq), Mg(OTf)₂ (10 mol%), 22 (11 mol%), ClCH₂CH₂Cl, rt</p>	 <p>(99), 72</p>	191
	<p>Acetyl cyanide (1.5 eq), catalyst <i>ent</i>-2b (1 mol%), toluene, -40°</p>	 <p>(86), 98</p>	188


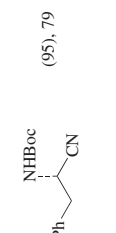
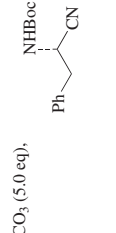
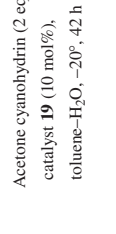

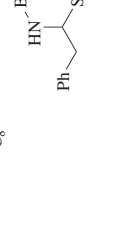
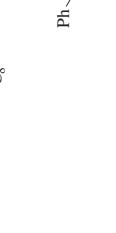


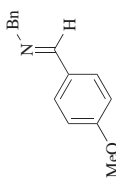
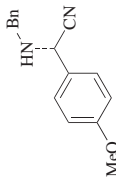
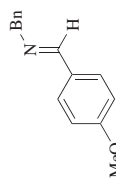
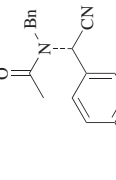
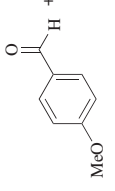
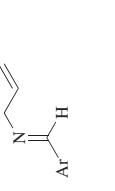
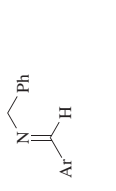
	Acetone cyanohydrin (2 eq), K ₂ CO ₃ (5.0 eq), catalyst 19 (10 mol%), toluene-H ₂ O, -20°, 42 h		(95), 79	186
	KCN (1.05 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 1 h		(93), 85	187
	KCN (1.05 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 1 h		(86), 86	187
	KCN (1.05 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 1 h		(96), 84	187
	KCN (1.05 eq), catalyst 4 (1 mol%), toluene-H ₂ O, 0°, 1 h		(96), 89	187
	HCN (1.5 eq), TADDOL (10 mol%), toluene, -40°, 3 d		(68), 30	193
	TMSCN (1.3 eq), Mg(OTf) ₂ (10 mol%), 22 (11 mol%), ClCH ₂ CH ₂ Cl, rt		R Me (99), 72 MeO (99), 84	191

TABLE 4. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES: NOV. 2006 TO AUG. 2007 (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	HCN (1.5 eq), TADDOL (10 mol%), toluene, -40°, 3 d	 (93), 22	193
	Acetyl cyanide (1.5 eq), catalyst ent-2b (1 mol%), toluene, -40°	 (95), 96	188
	Acetyl cyanide (1.5 eq), catalyst ent-2b (5 mol%), toluene, -40°, 36 h	I (88), 92	189
	HCN (2 eq), catalyst 21 (2 mol%), toluene, -50°, 24 h	Ar 2-MeC ₆ H ₄ (81), 69 3-MeC ₆ H ₄ (93), 78 4-MeC ₆ H ₄ (83), 75 2-MeOC ₆ H ₄ (98), 64 3-MeOC ₆ H ₄ (96), 66 4-MeOC ₆ H ₄ (79), 82	190
	HCN (1.2 eq), catalyst 20 (10 mol%), toluene, -40°, 4 h	Ar 4-MeC ₆ H ₄ (65), 70 3-MeC ₆ H ₄ (77), 74 2-MeC ₆ H ₄ (46), 52 3-MeOC ₆ H ₄ (70), 59 4-MeOC ₆ H ₄ (50), 51 3-CF ₃ C ₆ H ₄ (65), 31	192

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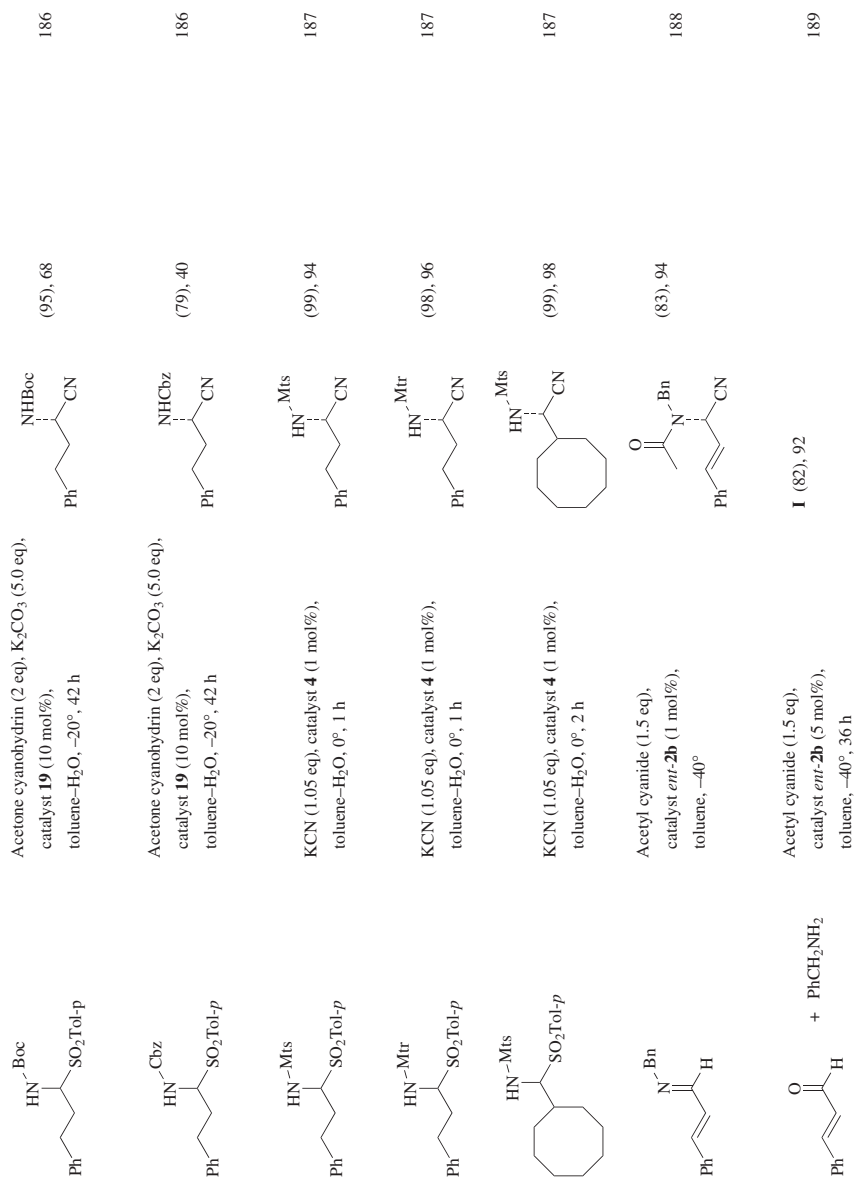
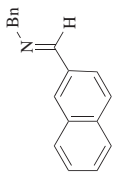
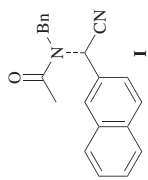
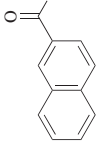

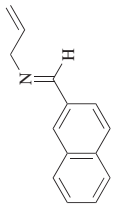
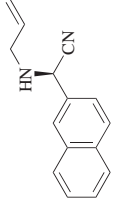
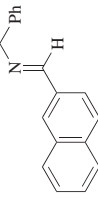
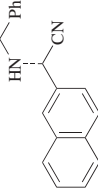
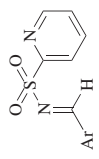
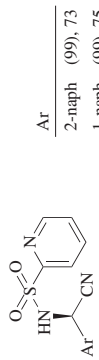
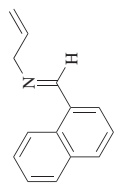
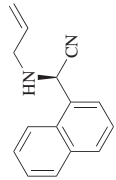


TABLE 4. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF ALDIMINES: NOV. 2006 TO AUG. 2007 (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	Acetyl cyanide (1.5 eq), catalyst ent-2b (1 mol%), toluene, -40°	 (92), 96	188
 + PhCH ₂ NH ₂	Acetyl cyanide (1.5 eq), catalyst ent-2b (5 mol%), toluene, -40°, 36 h	 I (92), 94	189
	HCN (2 eq), catalyst 21 (2 mol%), toluene, -50°, 24 h	 (73), 76	190
	HCN (1.2 eq), catalyst 20 (10 mol%), toluene, -40°, 4 h	 (46), 72	192
	TMSCN (1.3 eq), Mg(OTf) ₂ (10 mol%), 22 (11 mol%), ClCH ₂ CH ₂ Cl, rt	 Ar 2-naph (99), 73 1-naph (99), 75	191
	HCN (2 eq), catalyst 21 (2 mol%), toluene, -50°, 24 h	 (78), 80	190

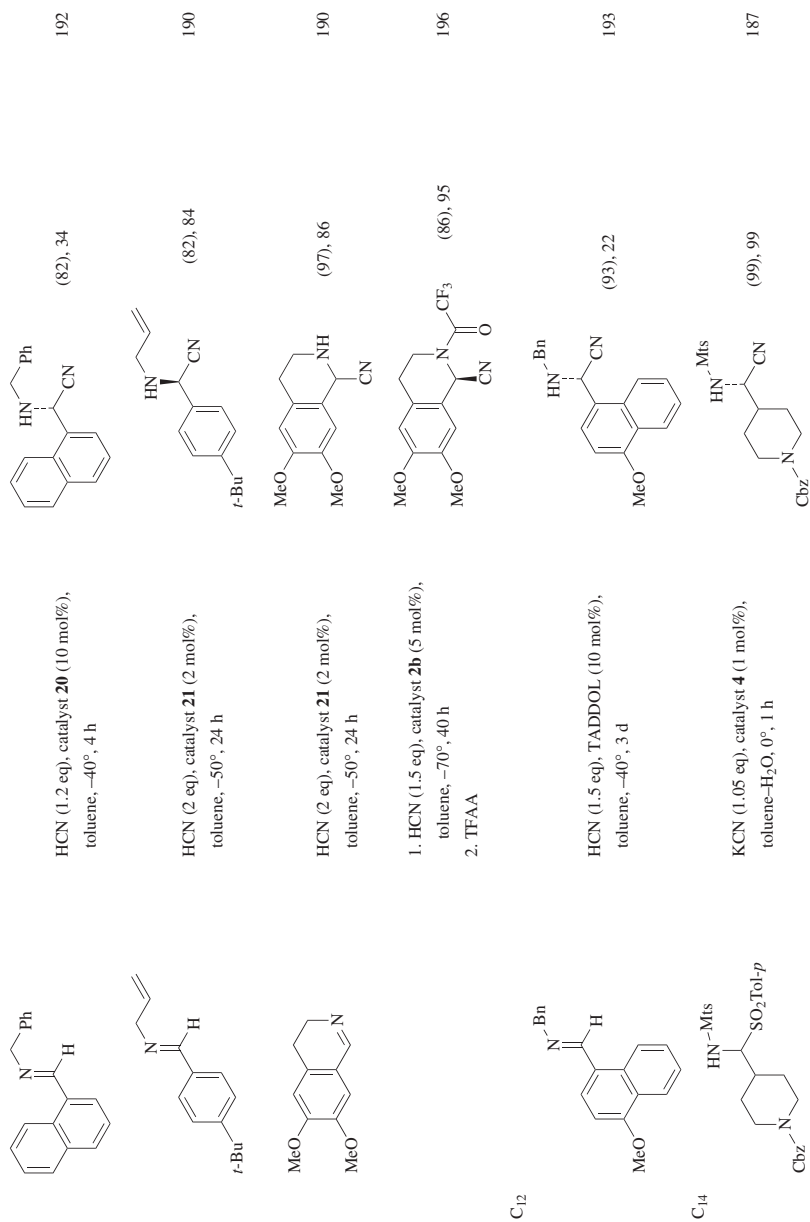
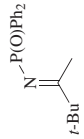



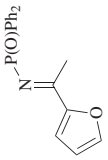
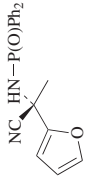
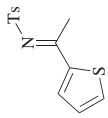
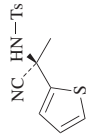
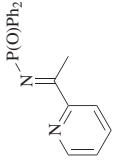
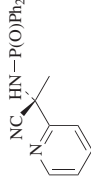
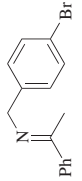
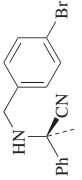
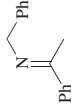

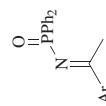



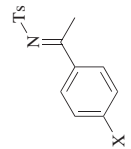
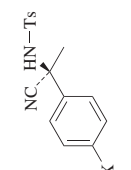
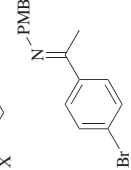
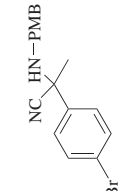
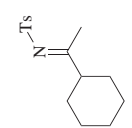
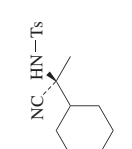
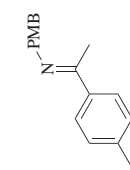
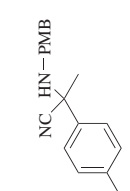


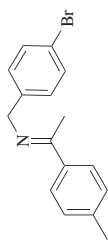
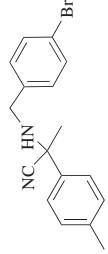
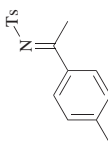
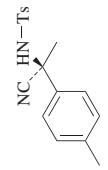
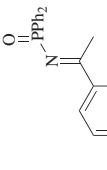


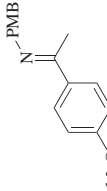
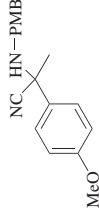
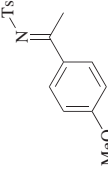
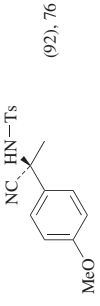
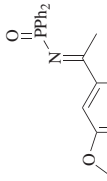
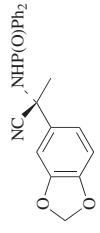
TABLE 5. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF KETIMINES; NOV. 2006 TO AUG. 2007

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
 C ₆	TMSCN (1.5 eq), catalyst 23 (5 mol%), toluene, -20°, 108 h	 (98), 80	194
 C ₆	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 70 h	 (95), 77	195
 C ₆	TMSCN (1.5 eq), catalyst 23 (5 mol%), toluene, -20°, 120 h	 (92), 77	194
 C ₆	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 80 h	 (92), 81	195
 C ₇	TMSCN (1.5 eq), catalyst 23 (5 mol%), toluene, -20°, 196 h	 (91), 72	194
 C ₈	HCN (2 eq), catalyst 21 (2 mol%), toluene, -50°, 24 h	 (63), 50	190
 C ₈	HCN (1.2 eq), catalyst <i>ent</i> - 20 (10 mol%), toluene, -40°, 4 h	 (92), 43	192

	TMSCN (1.5 eq), catalyst 23 (5 mol%), toluene, -20°		Ar Ph (91), 90 4-FC ₆ H ₄ (95), 90 4-ClC ₆ H ₄ (98), 89 4-BrC ₆ H ₄ (92), 91 3-ClC ₆ H ₄ (95), 88 3-O ₂ NC ₆ H ₄ (94), 88 2-FC ₆ H ₄ (98), 81	194
	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 68 h		NC, HN-Ts (99), 85	195
	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 80 h		X Cl (91), 71 Br (90), 71	195
	HCN (1.5 eq), catalyst 25 (5 mol%), toluene, -40°, 3 d		(88), 68	193
	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 68 h		NC, HN-Ts (99), 85	195
	HCN (1.5 eq), catalyst 25 (5 mol%), toluene, -40°, 3 d		NC, HN-PMB (90), 76	193

C₉

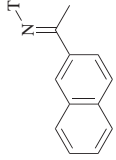
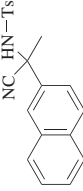
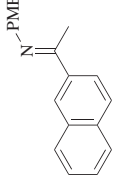
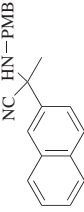
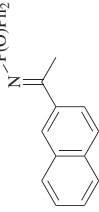
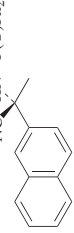
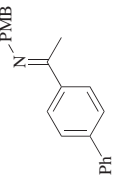
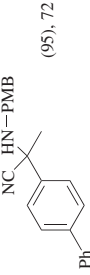
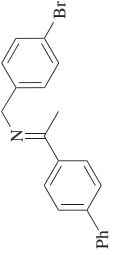
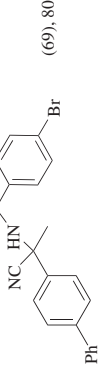
TABLE 5. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF KETIMINES; NOV. 2006 TO AUG. 2007 (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	HCN (1.5 eq), catalyst 25 (5 mol%), toluene, -40°, 3 d	 (89), 70	193
	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 80 h	 (94), 61	195
	TMSCN (1.5 eq), catalyst 23 (5 mol%), toluene, -20°	 (93), 89  (97), 92	194
	HCN (1.5 eq), catalyst 25 (5 mol%), toluene, -40°, 3 d	 (92), 56	193
	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 80 h	 (92), 76	195
	TMSCN (1.5 eq), catalyst 23 (5 mol%), toluene, -20°	 (91), 89	194



C₁₀

TABLE 5. CATALYTIC ENANTIOSELECTIVE STRECKER REACTIONS OF KETIMINES: NOV. 2006 TO AUG. 2007 (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%), % ee	Refs.
	TMSCN (1.5 eq), DAHQ (20 mol%), catalyst 24 (5 mol%), toluene, -20°, 80 h	 (98), 71	195
	HCN (1.5 eq), catalyst 25 (5 mol%), toluene, -40°, 3 d	 (82), 60	193
	TMSCN (1.5 eq), catalyst 23 (5 mol%), toluene, -20°, 168 h	 (90), 92	194
	HCN (1.5 eq), catalyst 25 (5 mol%), toluene, -40°, 3 d	 (95), 72	193
	HCN (1.5 eq), catalyst 25 (5 mol%), toluene, -40°, 3 d	 (69), 80	193

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