ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

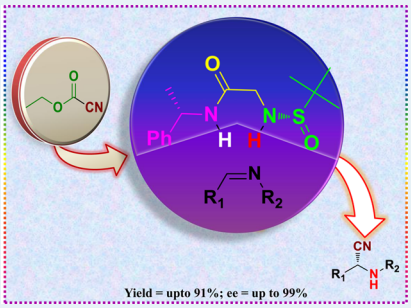
Small Molecule as a Chiral Organocatalyst for Asymmetric Strecker Reaction

S. Saravanan,[†,‡] Noor-ul H. Khan,*[,†,‡] Rukhsana I. Kureshy,[†,‡] Sayed H. R. Abdi,[†,‡] and Hari C. Bajaj[†,‡]

[†]Discipline of Inorganic Materials and Catalysis and [‡]Academy of Scientific and Industrial Research, Central Salt and Marine Chemicals Research Institute (CSMCRI), Council of Scientific & Industrial Research (CSIR), G. B. Marg, Bhavnagar-364 021, Gujarat, India

Supporting Information

ABSTRACT: A simple and novel chiral amide-based organocatalyst **6** was synthesized from readily available starting materials for the asymmetric Strecker reaction. A variety of *N*-benzhydryl- and *N*-tosyl-substituted imines were found to be suitable substrates with *i*-PrOH as an additive in the presence of chiral organocatalyst **6** at 0 °C with ethylcyanoformate as a source of cyanide for the synthesis of chiral α-amino nitriles. High yield (up to 91%) with excellent enantioselectivity (ee up to 99% of product) were achieved in 24−30 h in the case of both *N*-benzhydryl- and *N*-tosyl-substituted imines. To understand the mechanism of the catalytic Strecker reaction, NMR studies and kinetic investigations were carried out with different concentrations of the catalyst **6**, ethylcyanoformate, and substrate. It was found that the asymmetric Strecker reaction was first-order with respect to the concentration of the catalyst, EtOCOCN, and saturation kinetics in substrate. An appropriate stereochemical model for the enantioselective Strecker reaction is proposed. We further extend our study, using chiral α-amino nitriles [2-(benzhydrylamino)-2-(pyridin-3-yl)acetonitrile] for the synthesis of chiral amino amide and hydantoin in high yield with high enantioselectivity.



KEYWORDS: *Strecker reaction, organocatalyst, aldimines, enantioselective, amino amides*

INTRODUCTION

A standing area of interest in modern organic synthesis is to prepare optically active compounds which are often observed as fundamental building blocks for numerous applications. Chiral α-amino acids and their derivatives are a class of compounds that find use in a broad spectrum of applications, including synthesis,[1] catalysis,[2] and enzymology.[3] Among the diverse approaches, the asymmetric Strecker reaction is one of the most prominent, direct, and effective method for the synthesis of α-amino acids via hydrolysis of α-amino nitriles (Strecker product).[4] The state-of-the-art in the synthesis of chiral α-amino nitriles largely relies on both metal[5] and organo catalysts.[6] Various recent and past disclosures indicate that the organocatalyst-based protocols are preferred to avoid metal contamination; consequently, they have received a great deal of attention. Impressive organocatalytic systems such as Lipton's cyclic dipeptide, Corey's bicylic guanidine, Jacobsen's ureas and thioureas, Feng's *N*-oxides and bisformamides, and various Brønsted acids, carbohydrates, ammonium salts, amino acids, alkaloids, and phase transfer catalysts have been developed for this reaction.[6] Although the ground-breaking advances in the organocatalytic Strecker reaction are gratifying , there is still limited use of existing methodologies exemplifying drawbacks, such as the complex nature and multistep synthesis of the catalyst, the need for a very low temperature, and the requisite use of hazardous cyanide sources such as HCN, TMSCN, Bu_3SnCN, NaCN, and KCN. Mechanistically, a close examination of the preceding works has revealed that organocatalysts with the requisite stereogenic centers and ability to act as a hydrogen bond donor are efficient for the catalysis of hydrocyanation of imines in an enantioselective pathway. Thus, the designing of a simple (in terms of preparation) and highly effective chiral organocatalyst would be a major undertaking.

Recently, the chiral sulfinyl motif (R−S(O)−) has been shown to hold great promise as an important functional group for asymmetric synthesis because of its capability to transfer the chirality to a wide range of centers.[7] Despite the focused interest in the sulfinyl motif, the development of chiral sulfinamide as a chiral organocatalyst is still in its infancy, and furthermore, its application in the asymmetric Strecker reaction is scarce. Being intrigued by this motif, we conceptualized a design of an organocatalyst in which two different chiral moieties are appended with a spacer (Figure 1). Hypothetically, this design should provide reliable weak acidic sites with steric features and thereby be capable of interacting with the substrates in a stereogenic pathway. To our delight,

Figure 1. Design of the small molecule as a chiral organocatalyst.

Received: August 29, 2013
Revised: October 19, 2013
Published: October 22, 2013

Scheme 1. Synthesis of Catalyst 1

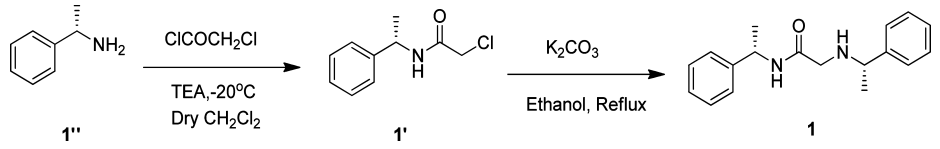
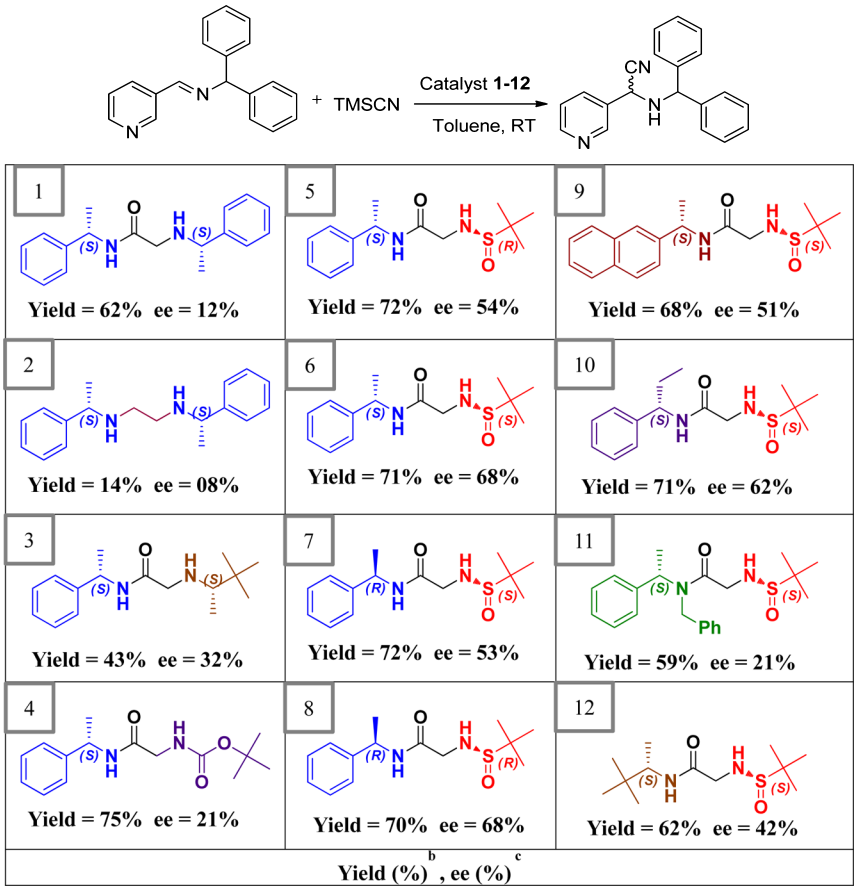


Table 1. Asymmetric Cyanation of Aldimine Catalyzed by Various Chiral Organocatalysts[a]



[a]Enantioselective Strecker reaction of substrate (0.10 mmol) was carried out with catalysts **1**−**12** (5 mol %) using TMSCN (0.15 mmol) as the source of cyanide. [b]Isolated yield. [c]ee's were determined by chiral HPLC using an AD-H column.

this new chiral organocatalyst is small and simple, easy to synthesize in two steps, and robust. The notable features of this system include a small molecule that can induce high enantioselectivities (up to 99%) in both *N*-benzhydryl- and *N*-tosyl-substituted imines under affordable reaction conditions such as catalyst loading (5 mol %) and temperature (0 °C to RT). Moreover, it is compatible to work efficiently with safer cyanide sources such as ethylcyanoformate.

RESULTS AND DISCUSSION

When designing the chiral organocatalyst, at the outset, we selected a starting material that is inexpensive and readily available, (*S*)-1-phenylethanamine, which, by introduction of a spacer (−$COCH_2$−) allows the formation of an amide−amine containing bifunctional catalyst **1**. This spacer offers several possible structural modifications to be explored for the development and fine-tuning of a chiral organocatalyst. This type of bifunctional catalyst was synthesized according to the following strategy (Scheme 1).

First, the commercial (*S*)-1-phenylethanamine was converted into the 2-chloro-*N*-(1-phenylethyl)acetamide **1′**, which on further treatment with potassium carbonate and (*S*)-1-phenylethanamine was refluxed in dry ethanol, resulting in bifunctional catalyst **1**.[8] Incidentally, other bases, such as NaH and TEA, do not give the desirable products in quantitative yields. Notably, catalyst **1** could easily be synthesized and fully characterized. With the successful synthesis of the catalyst, we started investigating the catalytic activity of **1** for the hydrocyanation of heterocylic derived *N*-benzhydryl imine as the benchmark reaction. It was found that a good yield of 62% with low enantioselectivity (12% ee) was obtained by employing 5 mol % of catalyst **1** (Table 1, entry 1). Although the result was inferior, it encouraged us to study further the structural modification of the catalyst, which incorporated the alteration of the spacer and requisite modification of the chiral scaffolds. In this regard, we attempted to change the spacer, which led to catalyst **2** (Table 1, entry 2) and which clearly discloses the necessity of a spacer containing the carbonyl moiety to form an amide scaffold. On the other hand, to check

dx.doi.org/10.1021/cs400742d | ACS Catal. 2013, 3, 2873−2880

the steric influences of a chiral amine, catalyst **3** was synthesized. It resulted in enhanced enantioselectivity, but it showed a deleterious effect on the yield (Table 1, entry 3). Moreover, it is understood from the body of literature available that the acidity and steric features of the organocatalyst influence the outcome of the reaction, in terms of both rate and enantioselectivity.[9]

On the basis of the precedents, we decided to assay the organocatalyst with two different amide moieties; thereby, catalyst **4** with a chiral amine and achiral amide appended with the spacer was synthesized. To our delight, the yield was improved (Table 1, entry 4). The enantioselectivity observed was moderate, revealing the necessity of two chiral centers bearing the amide groups to ensure this chiral sulfinamide motif was introduced to address the enantioinduction issue. In addition, it is well-known that the chiral sulfinamide motif bearing a −S═O− group interacts with the silicon; thereby, it facilitates liberation of HCN after the weak interaction with trimethylsilylcyanide.[10]

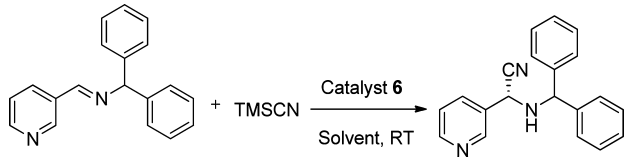
The organocatalyst **6** surrogate, the putative chiral urea type catalyst, was used for the Strecker reaction.[6e] A promising result (71% yield) with increased enantioselectivity (68%) was obtained using the chiral organocatalyst **6** (5 mol %) in the presence of toluene as the solvent. Switching over the chiral centers initiated the mismatching chirality in the catalysts **5** and **7** and gave products with lower ee's, 54% and 53%, respectively (Table 1, entries 5 and 7). The organocatalyst **8** with matching chiral centers (*R*, *R*) gave similar results with an inversion of the configuration in the product (Table 1, entry 8). Replacement of chiral 1-phenylethanamine with nonchiral 1-phenylethanamine led to a deteriorated enantiomeric excess, 21% with 70% yield. This unambigously indicates the need for chiral 1-phenylethanamine to catalyze the asymmetric Strecker reaction.

To evaluate further the activity of the catalyst, we decided to increase the steric factors of the catalyst by replacing the (*S*)-1-phenylethanamine of catalyst **6** with the bulkier (*S*)-1-(napthalen-2-yl)ethanamine **9** (68% yield, 51% ee), (*S*)-1-phenylpropanamine **10** (71% yield, 62% ee), and (*S*)-*N*-benzyl-1-phenylpropanamine **11** (59% yield, 21% ee) and the aliphatic (*S*)-3,3-dimethylbutan-2-amine **12** (62% yield, 42% ee). These fortuitous results clearly indicate that the chiral organocatalyst **6** with a flexible nature and conformationally appropriate functional groups with the requisite placement in space are key elements responsible for the potential activity of the catalyst in the asymmetric Strecker reaction.

Having identified **6** as the catalyst of choice, accordingly, optimization of the reaction conditions was investigated (Table 2) by varying the catalyst loading. The catalyst loading of 5 mol % used in the preceding experiments was found to be optimum because upon increasing the catalyst loading from 5 mol % to 10 mol %, the yield of the desired product was increased to 88% witha drop in ee of 55% (Table 2, entry 2). On the other hand, decreasing the catalyst loading (2.5 mol %) affects both the yield (59%) and ee (61%). Solvent screening showed that toluene was the best solvent (Table 2, entry 1). Other solvents, such as THF, CH_2Cl_2, and $CHCl_3$, gave lower enantioselectivities (Table 2, entries 4−6). Moreover, an attempt was made by using IPA as an additive to check its effect in the asymmetric Strecker reaction using TMSCN as a source of cyanide, and there was no significant enhancement in the reactivity, but the enantioselectivity was reduced (Table 2, entry 7).

These optimization studies did not result in the expected change in the enantioselectivity, so we attempted to modify the

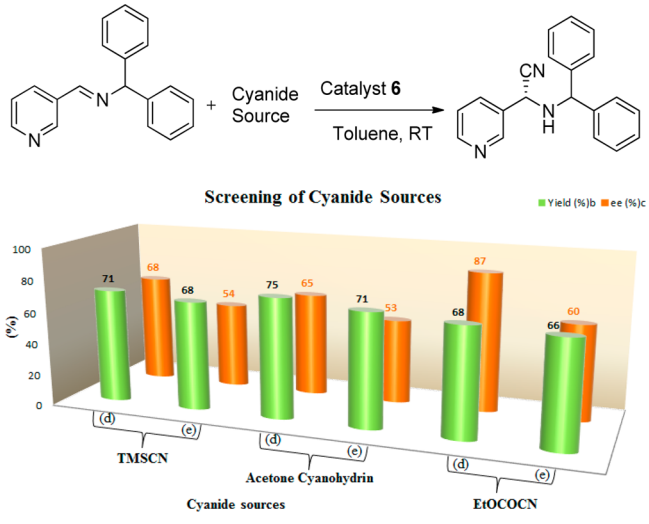
Table 2. Optimization Studies Using Chiral Organocatalyst 6 for the Asymmetric Strecker Reaction[a]



entry	catalyst (mol %)	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	5	toluene	8	71	68
2	10	toluene	8	88	55
3	2.5	toluene	8	59	61
4	5	THF	8	70	63
5	5	CH_2Cl_2	8	81	54
6	5	$CHCl_3$	8	79	51
7[d]	5	toluene	8	82	59

[a]Enantioselective Strecker reaction of substrate (0.10 mmol) was carried out with catalyst **6** using TMSCN (0.15 mmol) as the source of cyanide. [b]Isolated yield. [c]ee's were determined by chiral HPLC using an AD-H column. [d]Using 1.5 equiv of IPA as an additive.

sequence of addition and the cyanide sources (Figure 2). Although changing the sequence of addition, that is, instead of



[a]Enantioselective Strecker reaction of substrate (0.10 mmol) was carried out with catalyst **6**
[b]Isolated yield
[c]ee were determined by chiral HPLC using an AD-H column.
[d] Sequence of addition, catalyst **6** ← imine ← cyanide source.
[e] While reversing the sequence of addition i.e., catalyst **6** ← cyanide source ← imine.

Figure 2. Screening of cyanide sources for the asymmetric Strecker reaction catalyzed by chiral organocatalyst **6**[a].

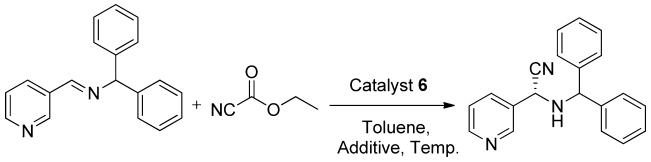
adding the imine to catalyst **6** followed by cyanide source (catalyst **6** ← imine ← cyanide source), we first added the cyanide source to the catalyst **6**, and then the imine was added (catalyst **6** ← cyanide source ← imine) which resulted in a drastic change in the enantioselectivity with all three cyanide sources (Figure 2e). This demonstrated that there is some interaction of the cyanide sources with catalyst **6**. The imine remains uninteracted with the catalyst, which leads to the achiral background reaction. To confirm this, ^{1}H NMR spectra were recorded, which showed that the cyanide source was interacting with the −S(O)−NH− and affected the substrate−catalyst vis-à-vis interactions (for details please see the Mechanism section, Figure 8). While using acetone cyanohy-

dx.doi.org/10.1021/cs400742d | ACS Catal. 2013, 3, 2873−2880

drin as the source of cyanide, no significant change in the yield and ee was observed in 8 h, but gratifyingly, while using ethylcyanoformate (EtOCOCN), the inexpensive and safer cyanide source, we could observe a vivid change in enantioselectivity (87%) in 12 h. Furthermore, for the sake of clarity, optimization of the enantioselective Strecker reaction using ethylcyanoformate was also carried out (see the Supporting Information)

The role of additives in the activity and enantioselectivity of the asymmetric Strecker reaction is well documented; therefore, we chose different protic solvents such as MeOH, EtOH, and *i*-PrOH (Table 3, entries 1−3) as a proton source. Evidently, the

Table 3. Asymmetric Strecker Reaction Catalyzed by Chiral Organocatalyst 6[a]



entry	additive	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	MeOH	RT	12	87	81
2	EtOH	RT	12	84	82
3	*i*-PrOH	RT	12	89	88
4	*i*-PrOH	0	24	87	97
5	*i*-PrOH	−10	24	84	95

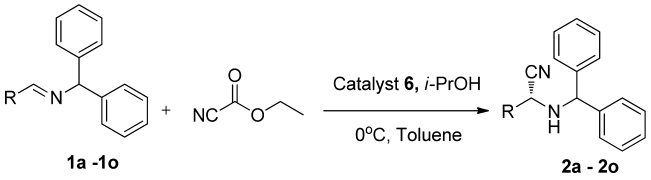
[a]The enantioselective Strecker reaction of the substrate (0.10 mmol) was carried out with catalyst **6** using TMSCN (0.15 mmol) as the source of cyanide. [b]Isolated yield. [c]ee's were determined by chiral HPLC using an AD-H column.

use of *i*-PrOH significantly improves the yield (89%) without affecting the enantioselectivity of the desired product (Table 3, entry 3). Because the enantioselective reactions are highly dependent on the temperature, we next investigated the Strecker reaction under different temperatures (RT, 0 °C and −10 °C). The best result was found at 0 °C (Table 3, entry 4). Further lowering the temperature is not beneficial in terms of yield and ee (Table 3, entry 5).

With the optimal conditions, the scope of the organocatalyst **6** was explored; the results are summarized in Tables 4 and 5. Interestingly, in the case of N-benzhydryl-substituted imine, which includes electron-donating and -withdrawing groups at ortho, meta, and para positions gave good to excellent enantioselectivity (ee, 81−99%, Table 4). Notably, aliphatic substrates were also found to be suitable for the asymmetric Strecker reaction using catalyst **6** (Table 4, entries 13−15).

Moreover, when attempts were made to conduct the asymmetric Strecker reaction with the bulkier *N*-tosyl-substituted imine having electron-donating and -withdrawing substituents at the ortho, meta, and para positions, excellent reactivity and enantioselectivity (Table 5) resulted. It indicates that the simple chiral organocatalyst **6** is capable of catalyzing a wide range of substrates to give an enantioselective Strecker product. The reaction was carried out at the 1 g scale using optimized reaction conditions, and it was found that the product formed in excellent yield with high enantioinduction (Table 4, entry 12). Conclusively, the orgnaocatalyst **6** was able to catalyze an asymmetric Strecker reaction using a wide range of substrates, including *N*-benzhydryl- and *N*-tosyl-substituted

Table 4. Scope of *N*-Benzhydryl-Substituted Imine Substrates for the Asymmetric Cyanation of Aldimines Catalyzed by Chiral Organocatalyst 6[a]

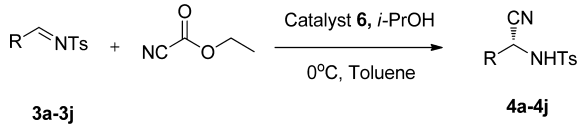


1a -1o 2a - 2o

entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5 (**2a**)	24	88	95 (*R*)[d]
2	4-Me-C_6H_4 (**2b**)	24	90	84
3	2-Me-C_6H_4 (**2c**)	24	88	99
4	3-Me-C_6H_4 (**2d**)	24	88	92
5	4-Br-C_6H_4 (**2e**)	28	86	99
6	2-Br-C_6H_4 (**2f**)	28	85	97
7	4-MeO-C_6H_4 (**2g**)	24	87	99
8	4-NO_2-C_6H_4 (**2h**)	30	84	93
9	2-NO_2-C_6H_4 (**2i**)	30	82	99
10	3-NO_2-C_6H_4 (**2j**)	30	82	94
11	2-F-C_6H_4 (**2k**)	24	82	82
12	3-pyridinyl (**2l**)	24	87 (89)[e]	97 (96)[e]
13	*tert*-butyl (**2m**)	30	81	94
14	$(CH_3CH_2)_2CH$ (**2n**)	30	84	81
15	$(CH_3)_2C{=}CH$ (**2o**)	30	79	82

[a]Enantioselective Strecker reaction of substrate (0.10 mmol) was carried out with catalyst **6** using EtOCOCN (0.15 mmol) as the source of cyanide. [b]Isolated yield. [c]ee's were determined by chiral HPLC using an AD-H and OD-H column. [d]Absolute configurations were assigned in comparison with a literature report[6p] and optical rotation. [e]Reaction conducted at 1 g scale under optimized condition.

Table 5. Scope of *N*-Tosyl-Substituted Imine Substrates for the Asymmetric Cyanation of Aldimines Catalyzed by Chiral Organocatalyst 6[a]



3a-3j 4a-4j

entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5 (**4a**)	30	88	91 (*R*)[d]
2	4-MeO-C_6H_4 (**4b**)	30	85	99
3	2-MeO-C_6H_4 (**4c**)	30	83	99
4	2-Me-C_6H_4 (**4d**)	30	81	99
5	2-F-C_6H_4 (**4e**)	30	85	98
6	2-naphthyl (**4f**)	30	87	91
7	4-Br-C_6H_4 (**4g**)	30	82	90
8	4-Me-C_6H_4 (**4h**)	30	86	99
9	3-Me-C_6H_4 (**4i**)	30	83	91
10	3-NO_2-C_6H_4 (**4j**)	30	80	99

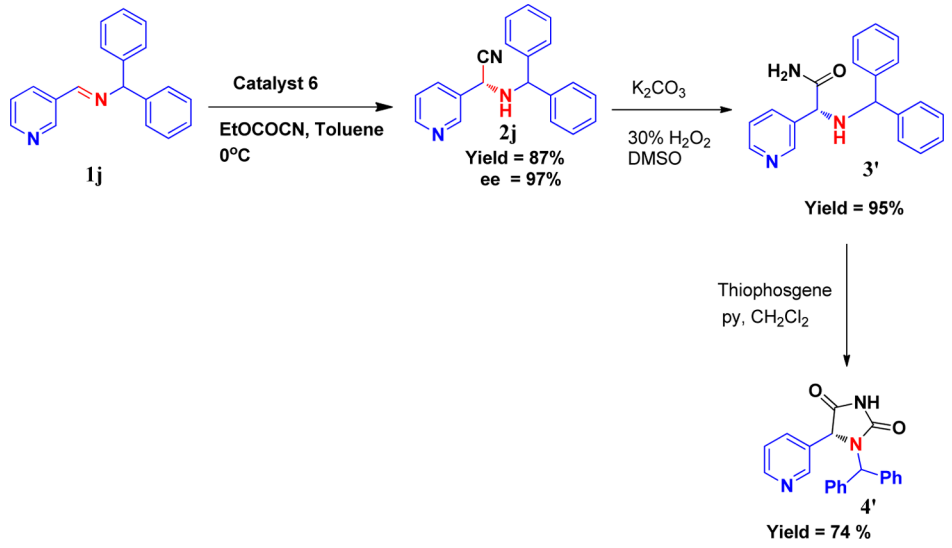
[a]Enantioselective Strecker reaction of substrate (0.10 mmol) was carried out with catalyst **6** using EtOCOCN (0.15 mmol) as the source of cyanide. [b]Isolated yield. [c]ee's were determined by chiral HPLC using an AD-H and OD-H column. [d]Absolute configurations were assigned in comparison with a literature report[5y] and optical rotation.

aldimines with excellent enantioselectivity for the desired product.

Applications. The present catalytic protocol using chiral organocatalyst **6** was successfully extended to the synthesis of

dx.doi.org/10.1021/cs400742d | *ACS Catal.* 2013, 3, 2873−2880

Scheme 2. Application of α-Amino Nitrile for the Synthesis of Chiral Amino Amides and Hydantoin



bioactive products, such as chiral amino amides and hydantoins. This compound was obtained in fewer steps with high yield and enantioselectivity (Scheme 2). Amino amides and hydantoins have been of considerable interest because they frequently contain a significant structural moiety found in various natural products, biologically active, and therapeutically useful compounds. Moreover, hydantoins substituted with heterocycles have played a key role in medicinal chemistry because their derivatives are associated with biological properties such as anticovascular, antidepressant, and antiviral activities.[11]

Kinetic Studies. To understand the mechanism of the hydrocyanation of an imine, kinetic experiments were performed with 1,1-diphenyl-*N*-(pyridin-3-ylmethylene)-methanamine, **2j**, as a model substrate and as a function of the concentration of catalyst **6** and substrate and using EtOCOCN as the source of cyanide. In all the kinetic runs, the plots of formation of the aminonitrile with time was found to be linear in the beginning of the reaction and attained saturation near its completion (Figure 3). On the basis of this observation, the initial rate constants, k_{obs}, were determined by directly estimating the amount of α-aminonitrile formed up to the completion of the reaction.

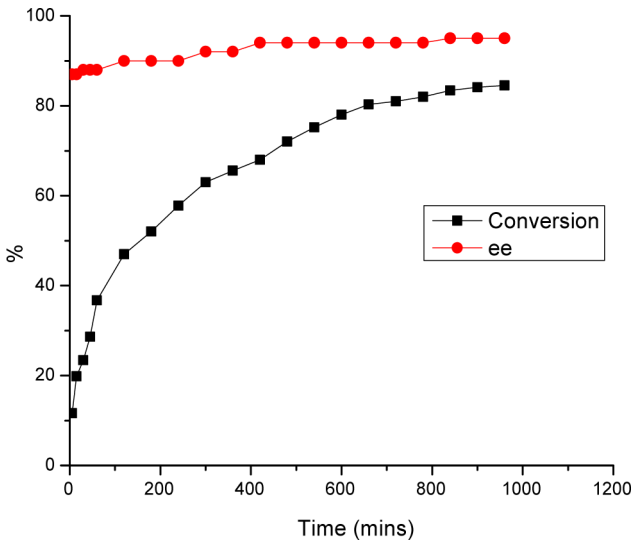


Figure 3. Time-dependent plot of the formation of α-aminonitrile.

Dependence of the Rate on the Catalyst Concentration. The Strecker reaction of imine **2j** was studied by conducting the kinetic experiments at different concentrations of catalyst **6** (0.001−0.006 M) at a constant concentration of pyrdine-derived *N*-benzhydrylimine (0.06 M) and EtOCOCN (0.09 M). From the kinetic data, a linear plot of k_{obs} of the α-aminonitrile formation versus log[catalyst] with unit slopes (d log k_{obs}/d log[catalyst] ∼ 1) was obtained, which passes through the origin, indicating that the Strecker reaction is of first-order with respect to the concentration of the catalyst (Figure 4).

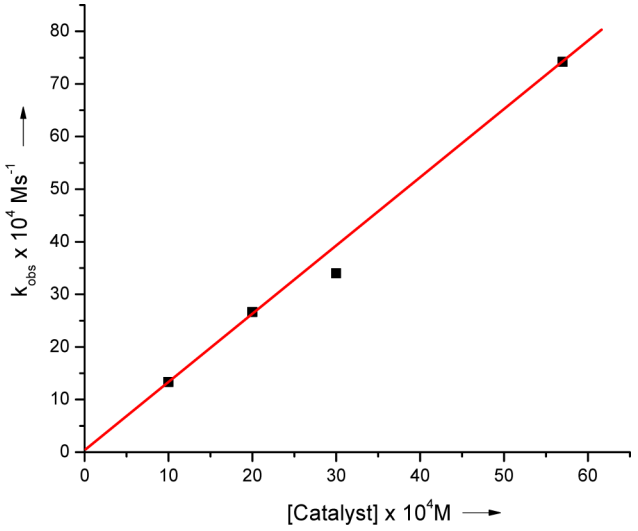


Figure 4. Plot of catalyst **6** concentration versus k_{obs} at 0 °C, [imine] = 0.06 M, [EtOCOCN] = 0.09 M.

Dependence of the Rate on Substrate Concentration. Kinetic experiments were carried out at different initial concentrations of imine **2j** ranging from 0.03 to 0.08 M by keeping the concentration of the other reactants and physical conditions constant, from which the rate was calculated and the plot of the rate constant (k_{obs}) versus the concentration of

dx.doi.org/10.1021/cs400742d | ACS Catal. 2013, 3, 2873−2880

substrate (d log k_{obs}/d log[substrate] ~ 1) was created, which showed the saturation kinetics with respect to the substrate concentration (Figure 5).

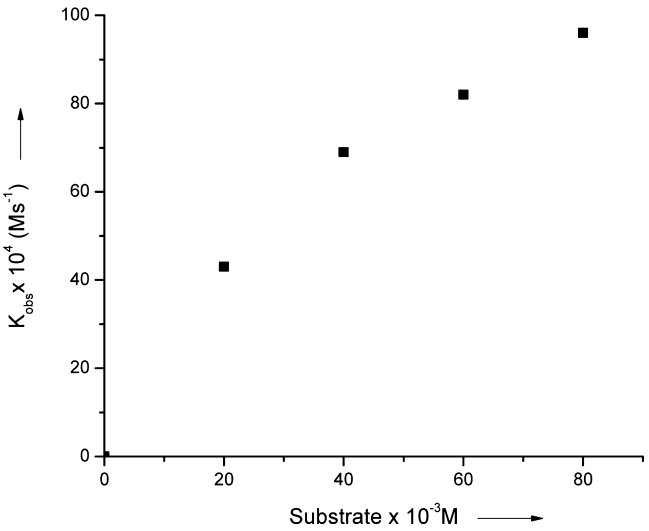


Figure 5. Plot of substrate concentration versus k_{obs} at 0 °C, [catalyst] = 0.003 M, [EtOCOCN] = 0.09 M.

Dependence of the Rate on EtOCOCN Concentration. The effect of the concentration of the EtOCOCN over the range of 0.01−0.15 M on the rate of the Strecker reaction of the imine **2j** were studied, keeping the catalyst (0.003 M) and imine (0.06 M) concentrations as constant, which also indicates the first-order dependence (d log k_{obs}/d log[EtOCOCN] ~ 1) in terms of the concentration of EtOCOCN (Figure 6).

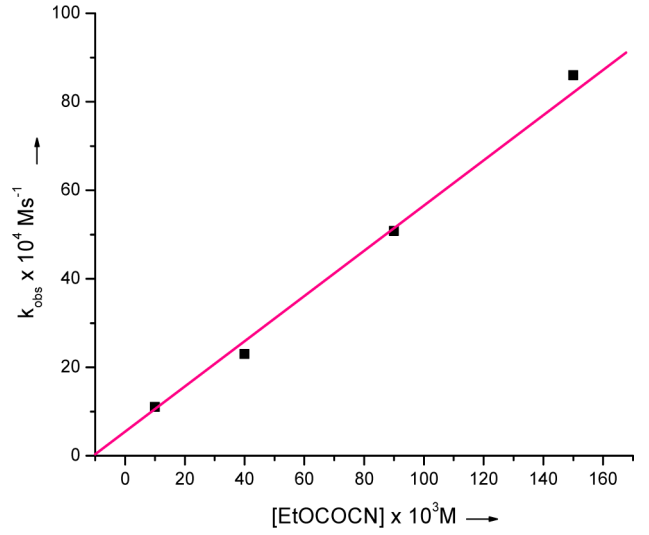


Figure 6. Plot of EtOCOCN versus k_{obs} at 0 °C, [catalyst **6**] = 0.003 M, [imine] = 0.06 M.

Overall, the kinetic data revealed a first-order dependence of the rate on EtOCOCN, catalyst **6**, and saturation kinetics with respect to the imine. On the basis of these data and conclusions drawn from the previous reports,[6e] a probable stereochemical model is proposed here (Figure 10).

Mechanism. To develop a useful understanding to ascertain the precise role of catalyst **6** in the Strecker reaction, we carried out kinetic studies of the hydrocyanation of imine and found that the transformation obeys Michaelis−Menten kinetics, with a first-order dependence on catalyst and cyanide source, EtOCOCN, and saturation kinetics with respect to imine. This result is similar to Jacobsen's thiourea system[6e] and clearly indicates that the imine catalyst binds through a bridge structure through hydrogen bonding. Moreover, a series of experiments and studies were carried out to understand the mechanism of the asymmetric Strecker reaction with the present simple chiral catalyst. At the outset, we tried to explore by conducting a series of NMR experiments in which we looked for the interaction of the catalyst with the substrate. From this, we understood that the *N*-H's of both the carbonyl and sulfonyl moieties were shifted upfield, clearly indicating that the imine was hooked up with catalyst **6** in a stereoselective manner (Figure 7 a,b). This unusual shift is mechanistically

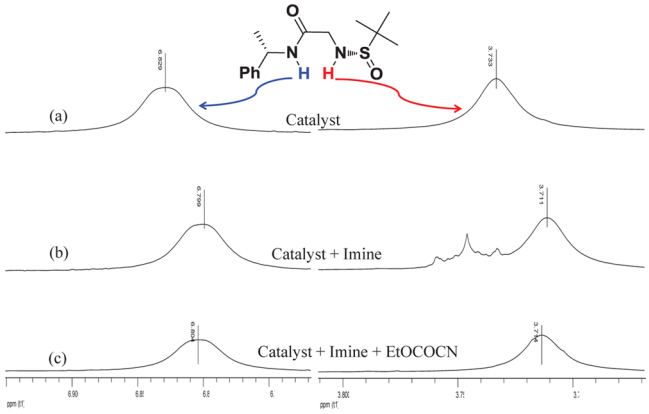


Figure 7. ^{1}H NMR spectra recorded in $CDCl_3$: (a) spectra represent sulfonyl N-**H** (3.733 ppm) and carbonyl N-**H** (6.829 ppm) of catalyst **6**; (b) catalyst **6** after interaction with imine; (c) catalyst **6** after interaction with imine and EtOCOCN.

akin to Jacobsen's[6e] model, in which an imine shifts back and forth between amide and sulfonamide protons. This was further confirmed by the observation of a downfield shift of the imine proton after interaction with the catalyst (Figure 8). In addition, after the addition of EtOCOCN to the catalyst−imine equilibrating structure, the *N*-H of both the carbonyl and sulfonyl moieties shifted downfield (Figure 7c). Moreover, when catalyst **6** was mixed with the cyanide source EtOCOCN, the *N*-H of the sulfinamide was shifted toward the downfield

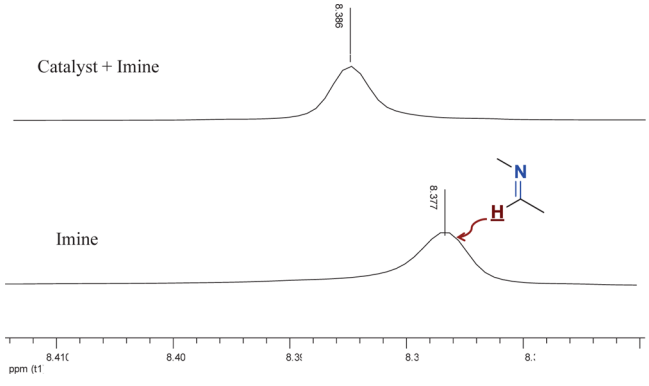


Figure 8. ^{1}H NMR spectra recorded in $CDCl_3$:imine (−C**H**═N−) after interaction with the catalyst.

dx.doi.org/10.1021/cs400742d | *ACS Catal.* 2013, 3, 2873−2880

region (Figure 9). That verifies that the EtOCOCN finds its suitable place during the catalytic process and releases the

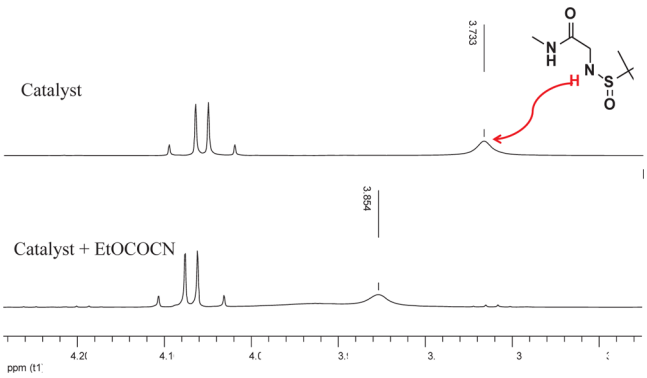


Figure 9. ^{1}H NMR spectra recorded in $CDCl_3$:catalyst **6** after interaction with the cyanide source, EtOCOCN.

cyanide in a stereochemical pathway. With these observations we have proposed a stereochemical model for the enantioselective Strecker reaction (Figure 10), where EtOCOCN is placed on the Si face of the substrate to give preferentially the *R* form of the product, which is line with the experimental results.

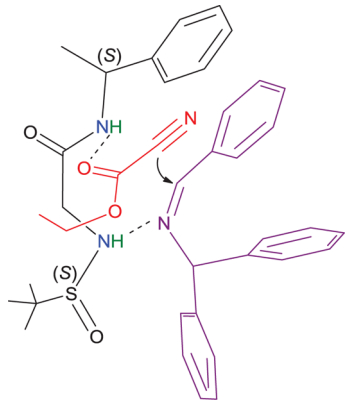


Figure 10. The proposed stereoselection model for the hydrocyanation of imines.

Recyclability of Catalyst 6. In general, homogeneous catalysts are not recycled because of their inherent problem of separation in the postcatalysis workup. However, it is prudent to attempt catalyst recyclability to know its stability under the reaction conditions.[12] In addition, the increased turnover number of the catalyst as a result of its successful reuse would offset the overall catalyst cost and make the protocol suitable for practical application. Therefore, reuse experiments were conducted using *N*-benzhydrylimine **2j** as a representative substrate with catalyst **6** (5 mol %) and ethyl cyanoformate as the source of cyanide at 0 °C using toluene as the solvent in the presence of *i*-PrOH. After the catalytic run, the amount of the solvent was reduced, and the organocatalyst **6** was precipitated by addition of an excess amount of *n*-hexane. The precipitate was then passed through a silica gel column to get the pure catalyst, which was then dried in vacuum, and used for the subsequent catalytic run. The recovered catalyst worked very well for the asymmetric Strecker reaction without any loss of its activity and enantioselectivity (Figure 11).

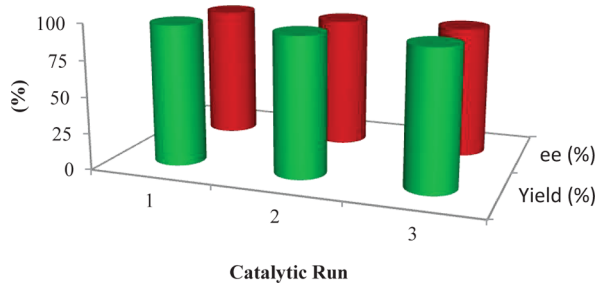


Figure 11. Recyclability of catalyst **6**.

CONCLUSION

This work has uncovered a new small and simple class of chiral amide-based organocatalyst that is highly efficient for the catalysis of the asymmetric Strecker reaction of *N*-benzhydryl- and *N*-tosyl-substituted imines using a safer cyanide source, EtOCOCN. Excellent enantioselectivities and good yields were achieved with a wide range of substrates. The kinetic investigations show first-order dependence on the concentrations of catalyst **6**, ethylcyanoformate, and saturation kinetics with respect to substrate. An appropriate stereoselection model for the asymmetric Strecker reaction is proposed. We further extend our study to the synthesis of bioactive compounds such as chiral amino amide and hydantoin in good yield and enantioselectivity.

EXPERIMENTAL SECTION

General. All the solvents were dried using standard procedures, distilled, and stored under nitrogen. NMR spectra were obtained with a Bruker F113 V spectrometer (200 and 500 MHz) and are referenced internally to trimethylsilane (TMS). Enantiomeric excess (ee) values were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD-H and OD-H chiral columns with 2-propanol/hexanes eluent. For the product purification, flash chromatography was performed using 230−400 mesh silica gel.

Typical Experimental Procedure for the Enantioselective Strecker Reaction of *N*-Substituted Imines Using Catalyst 6. In an oven dried reaction vial, catalyst **6** (5 mol %) and imine (0.2 mmol) were dissolved in dry toluene[12] (1 mL), and the resulting solution was stirred for 2 h at RT. Then the solution was cooled to 0 °C, and EtOCOCN (0.3 mmol) was added slowly over a period of 30 min, followed by the very slow addition of *i*-PrOH (20 μL). The reaction was monitored by TLC using hexane/ethyl acetate (90/10) as the eluent. After the reaction was complete, the solvent was removed on a rotavapor, and the product was purified by flash column chromatography on silica gel (eluted with hexane/ethyl acetate = 90:10). The purified products were characterized by ^{1}H NMR, which was in agreement with the reported values.[6p]

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H NMR, ^{13}C NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Fax: +91-0278-2566970. E-mail: khan251293@yahoo.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S. Saravanan and N. H. Khan are thankful to CSIR-SRF fellowship, DST, and CSIR Network Project on Catalysis for financial assistance. S.S. is thankful to AcSIR and also thankful to the Analytical Discipline and Centralized Instrument Facility of CSMCRI for providing instrumentation facilities.

■ REFERENCES

(1) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546. (b) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165. (c) Drauz, K.; Kleemann, A.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 584.
(2) (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (b) Lu, Y.; Johnston, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284. (c) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew.Chem., Int. Ed.* **2009**, *48*, 4288−4297. (d) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (e) Micskei, K.; Patonay, T.; Caglioti, L.; Palyi, G. *Chem. Biodiversity* **2010**, *7*, 1660. (f) Wang, H.-Y.; Zhang, J.-X.; Cao, D.-D.; Zhao, G. *ACS Catal.* **2013**, *3*, 2218−2221.
(3) (a) Liao, J. *Biotechnol. Prog.* **2007**, *23*, 28. (b) Noren, C. J.; Anthony-Cahill, S. J.; Griffith, M. C.; Schultz, P. G. *Science* **1989**, *244*, 182. (c) Wang, L.; Brock, A.; Herberich, B.; Schultz, P. G. *Science* **2001**, *292*, 498.
(4) (a) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27−51. (b) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584−4671. (c) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795−2828. (d) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947−6983. (e) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626−2704. (f) Fuertes, Y. P.; Taylor, J. E.; Tickell, D. A.; Mahon, M. F.; Bull, S. D.; James, T. D. *J. Org. Chem.* **2011**, *76*, 6038−6047. (g) Liu, Y.-L.; Zeng, X.-P.; Zhou, J. *Chem.—Asian J.* **2012**, *7*, 1759−1763.
(5) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315−5316. (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem.* **2000**, *112*, 1716. (c) Nogami, H.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 279−283. (d) Wang, J.; Hu, X. L.; Jiang, J.; Gou, S. H.; Huang, X.; Liu, X. H.; Feng, X. M. *Angew. Chem.* **2007**, *119*, 8620. (e) Wünnemann, S.; Fröhlich, R.; Hoppe, D. *Eur. J. Org. Chem.* **2008**, 684−692. (f) Krueger, C. A.; Kuntz, K. W.; Dzierb, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285. (g) Byrne, J. J.; Chavarot, M.; Chavant, P. Y.; Vallée, Y. *Tetrahedron Lett.* **2000**, *41*, 873−876. (h) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599. (i) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657−2658. (j) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem.* **1998**, *110*, 3369. (k) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762−767. (l) Kobayashi, S.; Ishitani, H. *Chirality* **2000**, *12*, 540−543. (m) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147−1150. (n) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634−5635. (o) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147−3151. (p) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153−3155. (q) Kato, N.; Mita, T.; Kanai, M.; Therrien, B.; Kawano, M.; Yamaguchi, K.; Danjo, H.; Sei, Y.; Sato, A.; Furusho, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6768−6769. (r) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652. (s) Saravanan, S.; Khan, N. H.; Bera, P. K.; Kureshy, R. I.; Abdi, S. H. R.; Kumari, P.; Bajaj, H. C. *ChemCatChem* **2013**, *5*, 1374−1385. (t) Khan, N. H.; Saravanan, S.; Kureshy, R. I.; Abdi, S. H. R.; Sadhukhan, A.; Bajaj, H. C. *J. Organomet. Chem.* **2010**, *695*, 1133. (u) Seayad, M. A.; Ramalingam, B.; Yoshinaga, K.; Nagata, T.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 264−267. (v) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 15118−15119. (w) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem.* **1998**, *110*, 3369. (x) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704−8708. (y) Wang, J.; Wang, W.; Li, W.; Hu, X.; Shen, K.; Tan, C.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 11642−11659. (z) Blacker, J.; Clutterbuck, L. A.; Crampton, M. R.; Grosjean, C.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1449−1456.
(6) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem.* **2000**, *112*, 1336; *Angew. Chem., Int. Ed.* **2000**, *39*, 1279−1281. (c) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−870. (d) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem.* **2007**, *119*, 618. (e) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014. (f) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968−971. (g) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919−1922. (h) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995−5000. (i) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (j) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358−15374. (k) Negru, M.; Schollmeyer, D.; Kunz, H. *Angew. Chem.* **2007**, *119*, 9500−9502; *Angew. Chem., Int. Ed.* **2007**, *46*, 9339. (l) Becker, C.; Hoben, C.; Kunz, H. *Adv. Synth. Catal.* **2007**, *349*, 417−424. (m) Wang, D.; Zhang, P. F.; Yu, B. *Helv. Chim. Acta* **2007**, *90*, 938. (n) Huang, X.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *Adv. Synth. Catal.* **2006**, *348*, 2579−2584. (o) Wen, Y.; Gao, B.; Fu, Y.; Dong, S.; Liu, X.; Feng, X. M. *Chem.—Eur. J.* **2008**, *14*, 6789−679. (p) Huang, J. L.; Liu, X. H.; Wen, Y. H.; Qin, B.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 204. (q) Hou, Z.; Wang, J.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2008**, *14*, 4484−4486. (r) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (s) Saravanan, S.; Sadhukhan, A.; Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Bajaj, H. C. *J. Org. Chem.* **2012**, *77*, 4375−4384. (t) Sadhukhan, A.; Saravanan, S.; Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Bajaj, H. C. *J. Org. Chem.* **2012**, *77*, 7076−7080. (u) Merino, P.; López, M.-E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219. (v) Martens, J. *ChemCatChem.* **2010**, *2*, 379−381. (w) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910−4911. (x) Liu, Y.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 4421−4423. (y) Liu, Y.-L.; Zhou, F.; Cao, J.-J.; Ji, C.-B.; Ding, M.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 3847−3850.
(7) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913−5915. (c) Beck, E. M.; Hyde, A. M.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 4260−4263. (d) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754.
(8) Orena, M.; Pori, G.; Sandri, S. *J. Org. Chem.* **1992**, *57*, 6533−6536.
(9) (a) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20678−20685. (b) Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194−7201.
(10) (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (b) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.
(11) (a) Mehta, N. B.; Diuguid, C. A. R.; Soroko, F. E. *J. Med. Chem.* **1981**, *24*, 465−468. (b) Gutschow, M.; Hecker, T.; Eger, K. *Synthesis* **1999**, 410−414. (c) Wessels, F. L.; Schwan, T. J.; Pong, S. F. *J. Pharm. Sci.* **1980**, *69*, 1102−1104. (d) Caldwell, A. G.; Harris, C. J.; Stepney, R.; Whittaker, N. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 495−505. (e) Roy, P.; Daniel, J. WO 2010/069069 A1.
(12) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. In *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: New York, 1981.