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Oxazoline-Based Organocatalyst for Enantioselective Strecker Reactions: A Protocol for the Synthesis of Levamisole

Arghya Sadhukhan,[a] Debashis Sahu,[b, c] Bishwajit Ganguly,*[b, c] Noor-ul H. Khan,*[a, c] Rukhsana I. Kureshy,[a, c] Sayed H. R. Abdi,[a, c] E. Suresh,[b, c] and Hari C. Bajaj[a, c]

Abstract: A chiral oxazoline-based organocatalyst has been found to efficiently catalyze asymmetric Strecker reactions of various aromatic and aliphatic *N*-benzhydrylimines with trimethylsilyl cyanide (TMSCN) as a cyanide source at −20 °C to give α-aminonitriles in high yield (96 %) with excellent chiral induction (up to 98 % *ee*). DFT calculations have been performed to rationalize the enantioselective formation of the product with the organocatalyst in these reactions. The organocatalyst has been characterized by single-crystal X-ray diffraction analysis, as well as by other analytical methods. This protocol has been extended to the synthesis of the pharmaceutically important drug molecule levamisole in high yield and with high enantioselectivity.

Keywords: aminonitriles · enantioselectivity · organocatalysis · oxazoline · Strecker reaction

Introduction

Chiral α-aminonitriles constitute a valuable class of compounds[1–4] and can be synthesized by an elegant asymmetric Strecker reaction.[5] Although in the last ten years both metal-containing[6] and metal-free[7] asymmetric Strecker reactions have been accomplished, metal-free protocols are desirable in the pharmaceutical industry in order to avoid metal contamination in the final drug formulations. Lipton et al.[8] in 1996 were the first to apply organocatalysis (a chiral cyclic dipeptide) to the asymmetric Strecker reaction, which was followed by various other organocatalysts, such as bicyclic guanidine,[9] ureas and thioureas,[10] carbohydrates,[11] *N*-oxides,[12] bisformamides,[13] ammonium salts,[14] Brønsted acids,[15] amino acids,[16] alkaloids,[17] and phase-transfer catalysts.[18,19] Close inspection of previous reports reveals that the activity of an organocatalyst mainly depends on weakly acidic sites capable of forming hydrogen bonds with the substrate, and at the same time weakly basic sites are also required in order to activate the cyanide source.[19] With this understanding, we designed an organocatalyst in which an oxazoline ring is appended to a sulfonamide group (Figure 1). Such a design should not only fulfill the requirement of acidic and basic sites, but also facilitate the construction of analogues with varying steric features, which is critical for practical application. Although oxazoline derivatives have been used as ligands with metals for various asymmetric transformations, they have been rarely used as organocatalysts.[20] The design of the present catalyst also allows flexibility in terms of creating chiral centers with matched or mismatched stereogenicity, which may have a bearing on the product enantioselectivity. As anticipated, all of the catalysts with the present design were found to be fairly active (product yield up to 93 %) at a moderate reaction temperature (−20 °C). However, the catalyst (*S*,*S*)-**1j** gave α-aminonitriles with excellent enantioselectivity (up to 98 % *ee* in some cases) with trimethylsilyl cyanide (TMSCN) as the cyanide source. We also extended the present

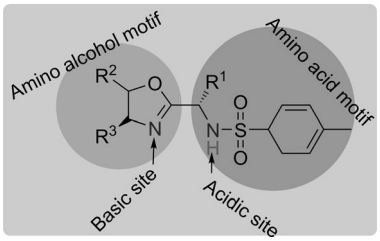

Figure 1. Structural features of the organocatalyst.

[a] A. Sadhukhan, Dr. N.-u. H. Khan, Dr. R. I. Kureshy, Dr. S. H. R. Abdi, Dr. H. C. Bajaj
Discipline of Inorganic Materials and Catalysis
Central Salt & Marine Chemicals Research Institute
(CSIR-CSMCRI)
G.B. Marg, Bhavnagar, 364002 (India)
E-mail: khan2512@yahoo.co.in

[b] D. Sahu, Dr. B. Ganguly, Dr. E. Suresh
Computation and Simulation Unit
(Analytical Discipline and Centralized Instrument Facility)
Central Salt & Marine Chemicals Research Institute
(CSIR-CSMCRI)
G.B. Marg, Bhavnagar, 364002 (India)
E-mail: ganguly@csmcri.org

[c] D. Sahu, Dr. B. Ganguly, Dr. N.-u. H. Khan, Dr. R. I. Kureshy, Dr. S. H. R. Abdi, Dr. E. Suresh, Dr. H. C. Bajaj
Academy of Scientific and Innovative Research
Central Salt & Marine Chemicals Research Institute
(CSIR-CSMCRI)
Bhavnagar, 364002 (India)

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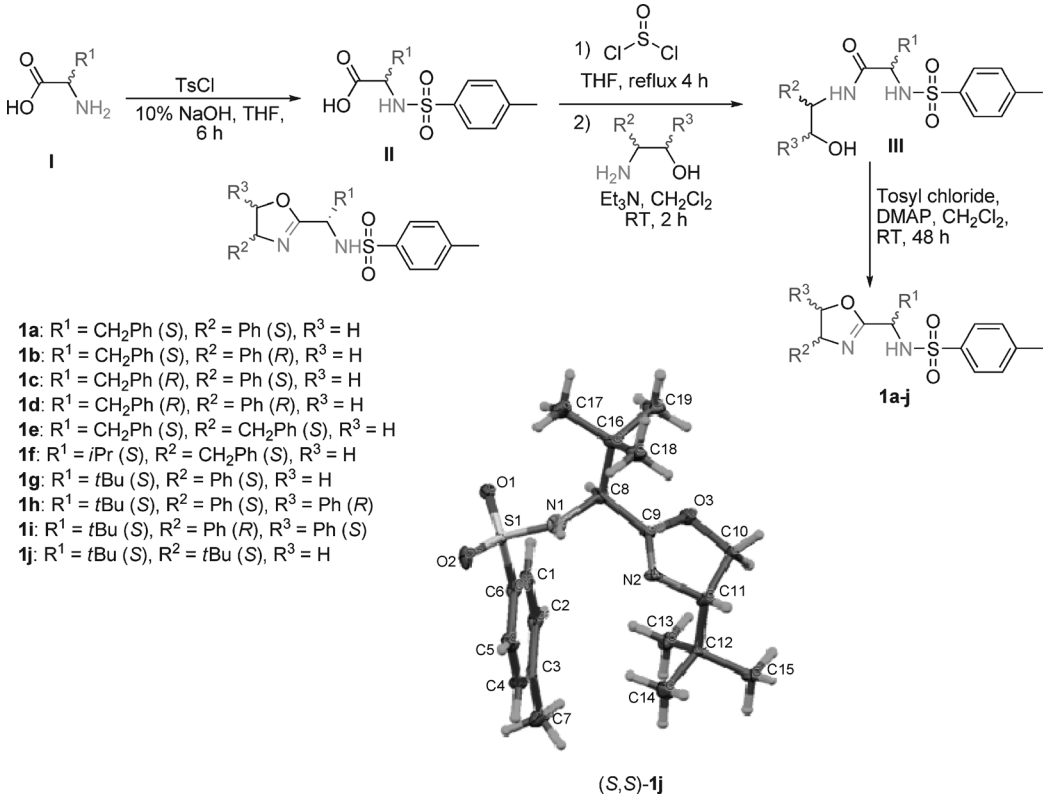
protocol to the synthesis of the chiral drug molecule levamisole.[21]

Results and Discussion

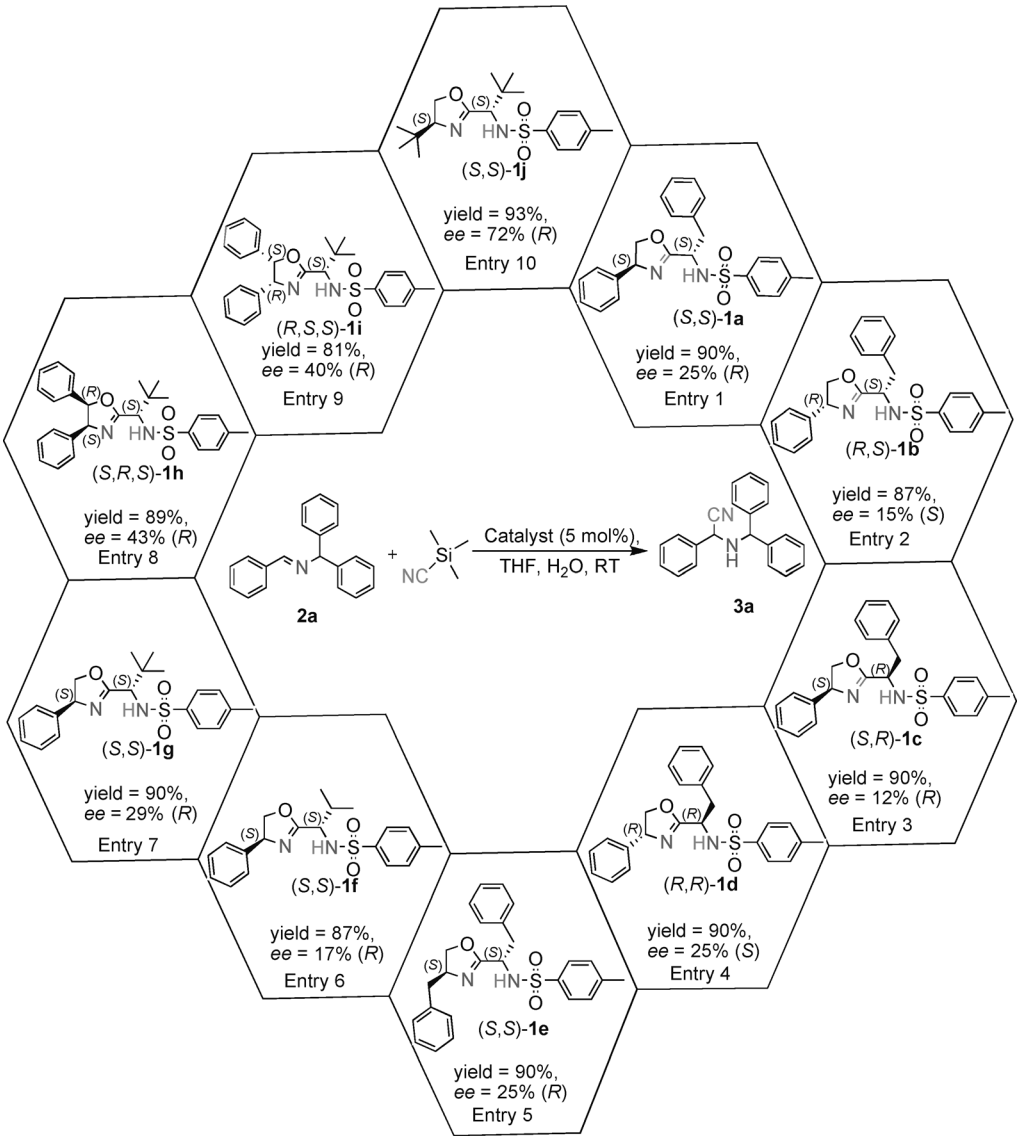
The organocatalysts **1a–j** were assembled by using chiral amino acids (**I**) and amino alcohols as basic building blocks according to Scheme 1. At first, various chiral amino acids having variable steric features were allowed to react with tosyl chloride. The resultant tosylated acids (**II**) were reacted with $SOCl_2$ to obtain the respective acid chlorides, which were directly reacted with various chiral amino alcohols to obtain the substituted chiral alkanolamides (**III**) in quantitative yields. Finally, oxazoline catalysts **1a–j** were prepared by cyclization of the corresponding amides **III** in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP).[22] A single crystal of organocatalyst (*S*,*S*)-**1j** obtained from dichloromethane/hexanes (1:2) was subjected to X-ray structure analysis[23] (Scheme 1). Characterization data are given in the Supporting Information, which proved useful for understanding the structures of intermediates involved in the Strecker reaction.

The catalysts **1a–j** were screened for their efficacy in the asymmetric Strecker reaction of *N*-benzhydrylimine (as a test substrate) by using TMSCN as a cyanide source in THF at room temperature (RT) in the presence of water as an additive and a source of protons, and the results are given in Scheme 2. It is evident from the results that all of the catalysts, **1a–j**, were highly efficient in catalyzing the Strecker reaction with the model substrate; however, not all of the catalysts showed good enantioselectivity. It can be seen from the results that catalysts with matching chiral centres gave products with higher *ee* values than their counterparts with mismatched chiral centres (e.g., entries 1 and 3). However, steric factors seem to be more pronounced; for example, catalyst **1f** bearing an isopropyl group (entry 6; 17% *ee*) was far less enantioselective than catalyst **1g** (entry 7; 29% *ee*) bearing a *tert*-butyl group at the same position on its amino acid motif. Among the catalysts synthesized for the present study, organocatalyst (*S*,*S*)-**1j** bearing two sterically demanding *tert*-butyl groups derived from both the amino acid and amino alcohol precursors was found to induce moderate enantioselectivity (72% *ee*) under the catalyst screening reaction conditions.

With these initial results with organocatalyst (*S*,*S*)-**1j**, we next worked on optimization of the reaction parameters in order to improve the results, particularly the enantioselectivity, using *N*-benzhydrylimine as a model substrate and TMSCN as the cyanide source at room temperature. The role of additives in the asymmetric Strecker reaction is well documented.[6] Therefore, we first explored the effect of different protic additives (mainly alcohols), specifically MeOH, EtOH, and isopropyl alcohol (IPA; 2.0 equiv; Table 1, en-



Scheme 1. Synthesis of catalysts and ORTEP diagram of oxazoline-based organocatalyst (*S*,*S*)-**1j** with atom numbering scheme (50% probability factor for the thermal ellipsoids).



Scheme 2. Screening of catalysts.

tries 1–3) on this reaction. Evidently, the use of IPA significantly improved the enantioselectivity (77% *ee*) of the product α-aminonitrile without affecting its yield. We next optimized the amount of IPA by keeping the other parameters constant (Table 1, entries 3–5).

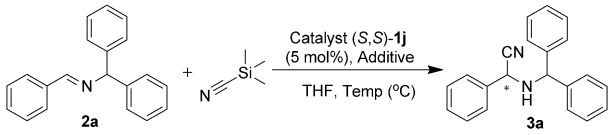
It was found that by lowering the IPA loading (1.0 equiv) there was a decrease in the product *ee* and yield, whereas with an increase in the amount of IPA (3.0 equiv) the reactivity increased, but the enantioselectivity decreased. Therefore, an additive loading of 2.0 equivalents was taken to be optimal (Table 1, entry 3).

Further, it was found that lowering the temperature to −20 °C had a beneficial effect on the product *ee* (92% compared with 77% at RT) although a longer reaction time was required (24 h compared with 12 h at RT). A further reduction in the temperature (−40 °C) did not have any positive impact on the product *ee* and, moreover, the reaction became very sluggish (36 h). Therefore, −20 °C was taken as optimal for further studies.

Additionally, the catalyst loading of 5 mol%, as used in the preceding experiments, was found to be optimal as it was observed that upon decreasing the catalyst loading (2.5 mol%) the product yield (75%) and *ee* (81%) dropped significantly. On the other hand, with an increase in catalyst loading (10 mol%), although the reaction was faster, there was a marginal drop in *ee* (87%), while the product yield remained the same (Table 2, entry 3).

To vary the solvent, CH_2Cl_2, $CHCl_3$, and THF were used to carry out the Strecker reaction under the above optimized conditions (Table 2, entries 4–6). However, THF remained the solvent of choice (Table 2, entry 1). Having established the reaction parameters for the use of catalyst (*S*,*S*)-**1j** in the asymmetric Strecker reaction with the reactants *N*-benzhydrylimine and TMSCN at −20 °C, we next

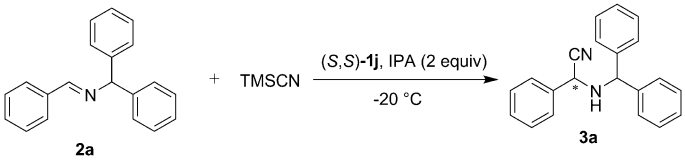
Table 1. Effect of additives and temperature on asymmetric Strecker reaction.[a]



Entry	Additive [equiv]	T [°C]	t [h]	Yield [%][b]	ee [%][c]
1	MeOH (2.0)	RT	12	87	58
2	EtOH (2.0)	RT	12	82	47
3	IPA (2.0)	RT	12	93	77
4	IPA (1.0)	RT	15	82	73
5	IPA (3.0)	RT	10	94	71
6	IPA (2.0)	0	24	90	85
7	IPA (2.0)	−20	24	90	90
8	IPA (2.0)	−40	36	80	89

[a] Enantioselective Strecker reaction of *N*-benzhydrylimine (0.25 mmol) was carried out with catalyst (*S*,*S*)-**1j** in toluene by using TMSCN (0.3 mmol) as a source of cyanide. [b] Yield of the isolated product. [c] The *ee* values were determined by chiral HPLC by using an AD-H column.

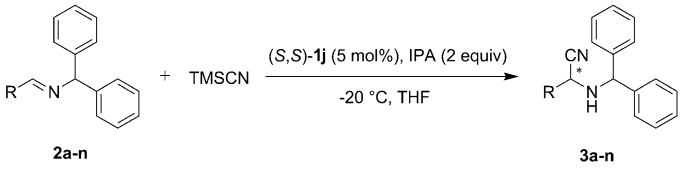
Table 2. Optimization of the appropriate catalyst loading (mol%) and effect of solvent for the asymmetric Strecker reaction.[a]



Entry	Catalyst loading [mol%]	Solvent	t [h]	Yield [%][b]	ee [%][c]
1	5	THF	24	90	90
2	2.5	THF	24	75	81
3	10	THF	24	88	87
4	10	CH_2Cl_2	12	93	67
5	10	$CHCl_3$	12	90	68
6	10	toluene	36	40	61

[a] Enantioselective Strecker reaction of *N*-benzhydrylimine (0.25 mmol) was carried out with catalyst (*S*,*S*)-**1j** by using TMSCN as a source of cyanide in the presence of IPA (2 equiv). [b] Yield of the isolated product. [c] The *ee* values were determined by chiral HPLC by using an AD-H column.

Table 3. Scope of substrates catalyzed by catalyst (*S*,*S*)-**1j**.[a]



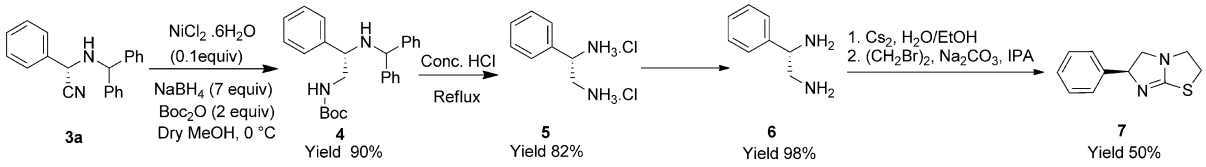
Entry	R	t [h]	Yield [%][b]	ee [%][c]
1	Ph (**2a**)	24	90	90 (*R*)[d]
2	2-MeC_6H_4 (**2b**)	24	90	94
3	2-MeOC_6H_4 (**2c**)	24	93	96
4	4-MeC_6H_4 (**2d**)	24	89	90
5	2-FC_6H_4 (**2e**)	24	78	91
6	2-ClC_6H_4 (**2f**)	20	90	82
7	2-BrC_6H_4 (**2g**)	20	93	80
8	2-O_2NC_6H_4 (**2h**)	24	90	82
9	2-naphthyl (**2i**)	24	96	98
10	2-thioenyl (**2j**)	24	94	82
11	3-pyridinyl (**2k**)	24	85	60
12	$PhCH_2$ (**2l**)	27	90	91
13	$PhCH_2CH$ (**2m**)	24	90	87
14	*tert*-butyl (**2n**)	24	91	93
15	isobutyl (**2o**)	24	94	90
16	hexyl (**2p**)	24	90	71
17	PhCH=CH (**2q**)	24	93	90
18	CH_3CH=CH (**2r**)	24	88	92
19	Ph (**2a**)	24	91	90 (*S*)[e]

[a] Enantioselective Strecker reaction of the imine (0.25 mmol) was carried out with catalyst (*S*,*S*)-**1j** by using TMSCN (0.3 mmol) as a source of cyanide in the presence of IPA (2 equiv). [b] Yield of the isolated product. [c] The *ee* values were determined by chiral HPLC by using AD-H and OD-H columns. [d] Absolute configurations were assigned by comparison with literature reports[5] and on the basis of optical rotation. [e] Reaction was carried out with the catalyst (*R*,*R*)-**1j**.

extended this protocol to imine substrates bearing various substituents on the phenyl group derived from the aldehyde precursor (Table 3, entries 2–8).

In general, electron-donating substituents resulted in better *ee* values in the product (90–96%; Table 3, entries 2–4) than electron-withdrawing groups (80–82% *ee*; Table 3, entries 6–8), with the exception of the fluoro-substituted imine, with which 91% *ee* was obtained, albeit with lower product yield (78%). The best *ee* value (98%) and yield (96%) were obtained with the bulkier naphthyl-derived imine (Table 3, entry 9). The presence of heteroatoms (S and N, Table 3, entries 10 and 11), particularly of nitrogen in the aromatic ring, significantly reduced the product *ee* value (60%, Table 3, entry 11), possibly due to the additional basic center that would also be involved in the activation of HCN (generated in situ) and would trigger a parallel Strecker loop. Aliphatic substrates, including phenyl-substituted alkyl substrates (Table 3, entries 12–16), also gave very good product yields (90–94%) and *ee* values (71–93%). We also checked the generality of the catalyst with enolizable imines (Table 3, entries 17 and 18) and we achieved very good product yields of up to 93% and *ee* values of up to 92%. Finally, we used the opposite configuration of the catalyst with substrate **2a** under similar reaction conditions and obtained exactly the same results with opposite configuration of the product. This gave us very good flexibility in terms of selecting the appropriate chirality of the catalyst for the required product, which we demonstrated by the synthesis of the powerful anthelmintic drug levamisole by using the present protocol.

Application of the catalyst to the synthesis of levamisole: The present asymmetric catalytic Strecker protocol with the chiral-oxazoline based organocatalyst (*R*,*R*)-**1j** was successfully extended to the synthesis of the pharmaceutically important drug molecule levamisole (Scheme 3). Compound **7** was obtained in fewer steps than previously, in high yield



Scheme 3. Transformation of a chiral α-aminonitrile into levamisole.

and with high enantioselectivity (experimental procedures and characterization data are provided in the Supporting Information).

Kinetic study: To understand the mechanism of the hydrocyanation of imines, kinetic experiments as a function of the concentration of catalyst (*S,S*)-**1j** were performed with imine **2a** as a model substrate and TMSCN as a source of cyanide. For all of the kinetic runs, plots of the formation of α-aminonitrile versus time were found to be initially linear, but were indicative of saturation near completion (Figure 2).

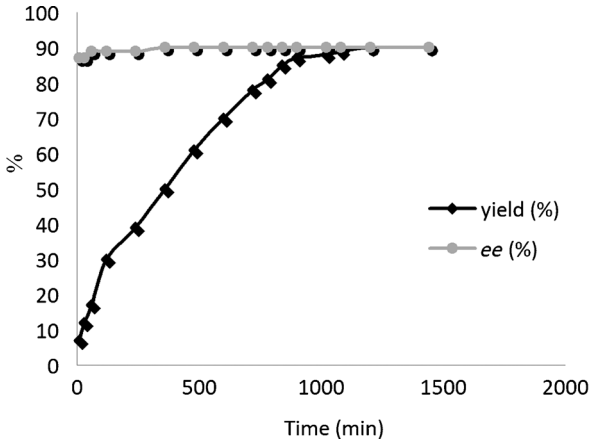


Figure 2. Temporal evolution of the formation of α-aminonitrile at −20 °C.

Based on this observation, the initial rate constants k_{obs} were determined by directly estimating the amount of α-aminonitrile formed up to completion of the reaction. Initially, we carried out kinetic experiments at different concentrations of catalyst (*S,S*)-**1j** (0.003–0.024 mM) and constant concentrations of imine (0.48 mM) and TMSCN (1.92 mM). From the kinetic data, a linear plot of k_{obs} of α-aminonitrile formation versus log[catalyst] with unit slope ($d\log k_{obs}/d\log[\text{catalyst}] \approx 1$) that passes through the origin was obtained, indicating that the Strecker reaction follows first-order kinetics with respect to the concentration of the catalyst (Figure 3).

Next, we performed kinetic experiments at different initial concentrations of imine **2a** in the range 0.12–0.96 mM, keeping the concentration of the catalyst (0.012 mM) and TMSCN (1.92 mM) and the physical conditions unchanged. The rate was calculated and a plot of k_{obs} versus the concentration of substrate ($d\log k_{obs}/d\log[\text{substrate}] \approx 1$) showed first-order dependence of the process on the substrate concentration (Figure 4). Finally, the effect of the concentration of TMSCN over the range 0.48–3.84 mM on the rate of the Strecker reaction of imine **2a** was studied, keeping the catalyst (0.012 mM) and imine (0.48 mM) concentrations constant. First-order dependence ($d\log k_{obs}/d\log[\text{TMSCN}] \approx 1$) was observed (Figure 5). Overall, the kinetic data revealed first-order dependences on TMSCN, substrate **2a**, and catalyst (*S,S*)-**1j**.

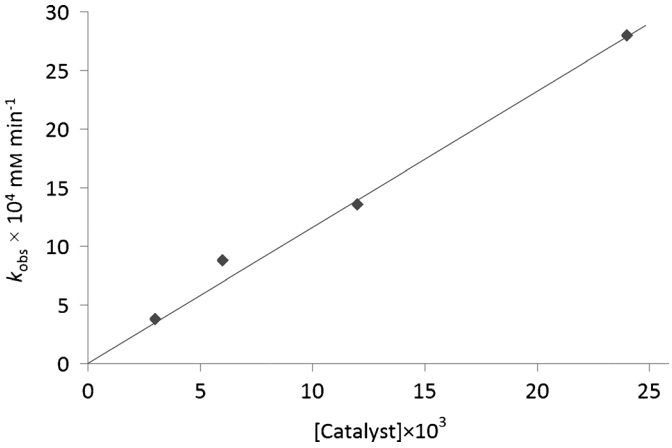


Figure 3. Plot of catalyst (*S,S*)-**1j** concentration versus k_{obs} at −20 °C, [imine] = 0.48 mM, [TMSCN] = 1.92 mM.

DFT calculations: A density functional theory (DFT) study was performed to examine the formation of an enantiomeric excess of (*R*)-α-aminonitriles in the Strecker reaction with imines, specifically the hydrocyanation of *N*-benzhydrylimine, by the chiral oxazoline-based organocatalyst. B3LYP-D/6-31G(d)//B3LYP/6-31G(d) calculations were performed with the imine substrate (**2a**) and organocatalyst (*S,S*)-**1j** as a representative case to explore the mechanism of this Strecker reaction. Recently, for computational studies on organocatalytic reactions, B3LYP methods have been used[12e] and the results have been in excellent agreement with experimental observations.[24–27] We have also considered dispersion corrections in the calculations at the B3LYP/6-31G(d) level.[28] The crystal structure of the chiral oxazoline-based organocatalyst (*S,S*)-**1j** was used to model the reactions.

In the asymmetric Strecker reaction, HCN is generated in situ by the addition of controlled amounts of an alcohol to a solution of TMSCN in an appropriate solvent.[10f,j] Generally, the accepted mechanism for the Strecker reaction in-

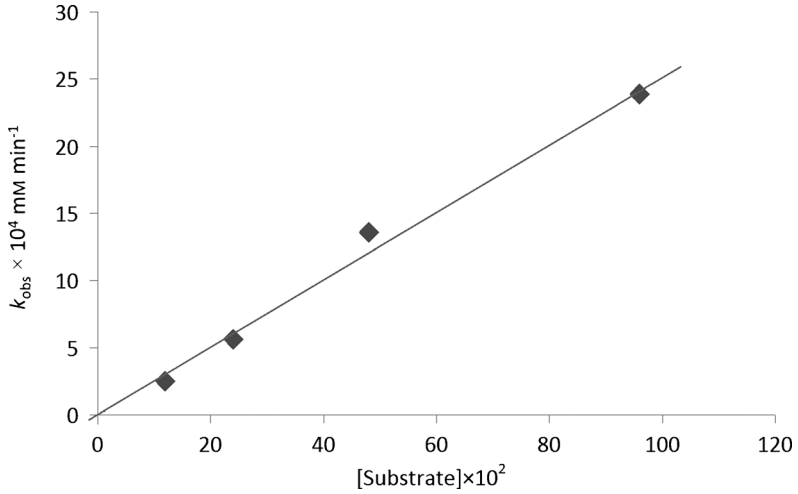


Figure 4. Plot of substrate imine **2a** concentration versus k_{obs} at −20 °C, [catalyst] = 0.012 mM, [TMSCN] = 1.92 mM.

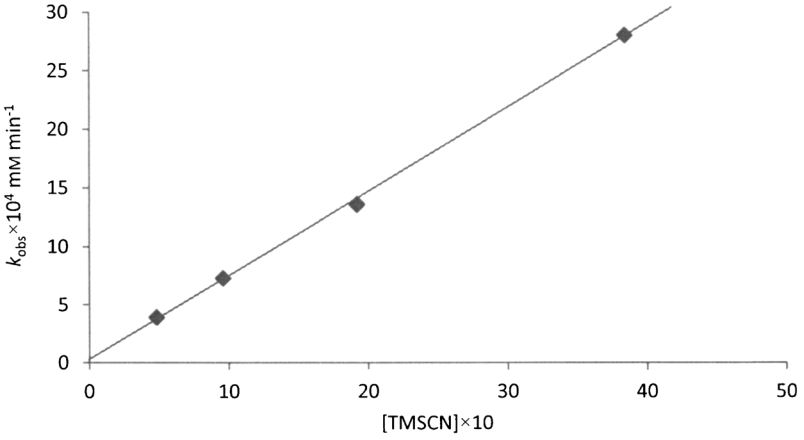


Figure 5. Plot of substrate TMSCN concentration versus k_{obs} at −20 °C, [catalyst] = 0.012 mM, [imine] = 0.48 mM.

volves the isomerization and activation of HCN in the presence of the catalyst.[29] The isomerization of the nascent HCN is a highly energetic process. The activation barrier calculated for the isomerization of HCN to HNC at the B3LYP-D/6-31G(d)//B3LYP/6-31G(d) level of theory is 217.38 kJ mol^{-1} (Figure 6), which is in good agreement with a previously reported value.[30] However, the generated HNC is more reactive than HCN in the reaction medium[31] because it is energetically less stable than the latter by 72.29 kJ mol^{-1} (Figure 6).[32–34]

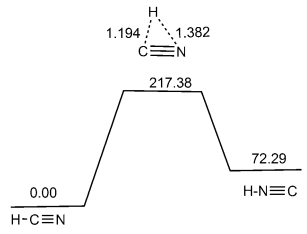


Figure 6. Relative energy profile [kJ mol^{-1}] for the isomerization of HCN to HNC in THF medium computed at the B3LYP-D/6-31G(d)//B3LYP/6-31G(d) level of theory. All the distances are in Å.

It has been reported that an organocatalyst can reduce the activation barrier for the isomerization of HCN to HNC in Strecker reactions.[30] The crystal structure of the chiral oxazoline-based organocatalyst (*S*,*S*)-**1j** was employed to examine the isomerization process of HCN to HNC at the B3LYP-D/6-31G(d)//B3LYP/6-31G(d) level of theory. The calculated results showed the transition state for the isomerization of HCN to HNC to be 7.72 kJ mol^{-1} higher in energy than the separated reactants (Figure 7). HNC complexed with the organocatalyst (*S*,*S*)-**1j** (complex 2) is energetically less stable than complex 1 and hence a reactive species for further reaction.

Experimental study of the hydrocyanation reaction of *N*-benzhydrylimine (**2a**) in the presence of organocatalyst (*S*,*S*)-**1j** showed that the (*R*)-α-aminonitrile is favored over the corresponding (*S*)-α-aminonitrile. To examine the preferential formation of (*R*)-α-aminonitriles, by using the chiral oxazoline-based organocatalyst (*S*,*S*)-**1j** complex (complex 2) for this Strecker reaction with *N*-benzhydrylimine, transition states were located for both the *R* and *S* configurations (Figure 8).

The B3LYP-D/6-31G(d)-calculated relative energies show that the transition state (TS) of the *R* configuration is 20.58 kJ mol^{-1} more stable than that of the corresponding *S* configuration in the THF medium. From the transition-state geometries, it is evident that strong N−H···N hydrogen bonding (2.132 Å) is present between the imine substrate and the oxazoline-based chiral catalyst in the (*R*)-TS (Figure 8).[35,36] The N−H···N hydrogen-bond length in the (*S*)-TS is much longer (3.898 Å). These calculated results show that the strong N−H···N hydrogen bonding is primarily responsible for stabilizing the (*R*)-TS compared to the (*S*)-TS, thus rationalizing the experimental result of higher *ee* for (*R*)-α-aminonitriles over (*S*)-α-aminonitriles for this Strecker reaction.

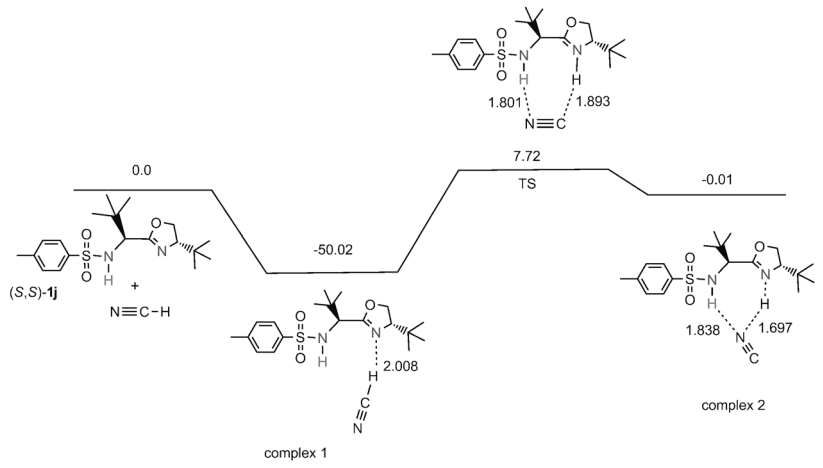
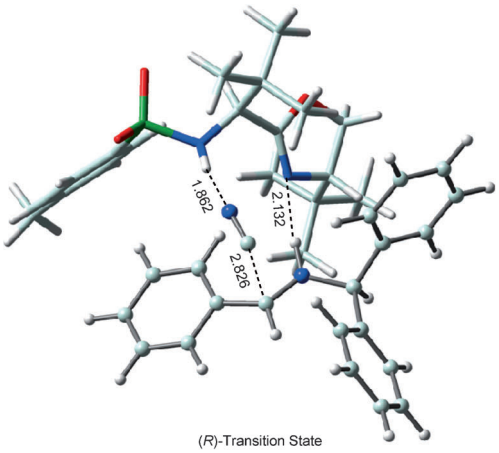


Figure 7. Relative energy profile [kJ mol^{-1}] for the isomerization of HCN to HNC mediated by organocatalyst (*S*,*S*)-**1j** in THF medium computed at the B3LYP-D/6-31G(d)//B3LYP/6-31G(d) level of theory. All the distances are in Å.



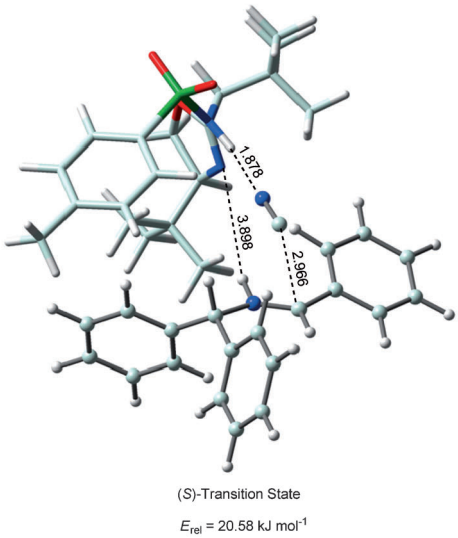


Figure 8. B3LYP-D/6-31G(d)//B3LYP/6-31G(d)-calculated transition-state geometries of the (*R*)- and (*S*)-enantiomeric forms with their relative energy values in THF medium. All the distances are in Å. [Pale blue = carbon; white = hydrogen; red = oxygen; blue = nitrogen; green = sulfur].

Conclusion

The chiral organocatalyst (*S*,*S*)-**1j** is highly efficient in catalyzing the asymmetric Strecker reaction of aromatic and aliphatic aldimines with TMSCN as a source of cyanide. High yields and *ee* values have been achieved with a wide range of substrates. The catalyst (*S*,*S*)-**1j** has also been successfully employed in the synthesis of the pharmaceutically important drug levamisole in good yield and with high enantioselectivity in a few steps. DFT calculations have been performed to rationalize the formation of (*R*)-α-aminonitriles in higher *ee* than (*S*)-α-aminonitriles in this Strecker reaction. Strong N–H···N hydrogen bonding between the catalyst and the substrate is primarily responsible for stabilizing the (*R*)-TS compared to the (*S*)-TS, which provides a rationale for the experimental results.

Experimental Section

General: All solvents were dried by using standard procedures, distilled, and stored under nitrogen. NMR spectra were obtained on a Bruker F113 V spectrometer (200 and 500 MHz) and referenced internally to tetramethylsilane (TMS). Enantiomeric excess (*ee*) values were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD, AD-H, OD-H, and OD chiral columns with 2-propanol/hexane as eluent. Products were purified by flash column chromatography on silica gel of 230–400 mesh.

Typical experimental procedure for the enantioselective Strecker reaction of *N*-benzhydrylimines by using catalyst (*S*,*S*)-1j: In a reaction vial, catalyst (*S*,*S*)-**1j** (5 mol %) and the imine (0.25 mmol) were dissolved in THF (1 mL) and the solution was stirred for 1 h at RT. It was then cooled to −20 °C and TMSCN (0.3 mmol) was slowly added over a period of 2 h, which was followed by the very slow addition of IPA (0.6 mmol). The reaction was monitored by TLC, eluting with hexane/ethyl acetate (90:10). On completion of the reaction, the solvent was removed on a rotavapor and the product was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 90:10). The purified products were characterized by ^{1}H NMR spectroscopy and the spectra were in agreement with those reported previously.[5]

Computational methods: Full geometrical optimizations were carried out in the gas phase employing the Becke three-parameter hybrid density functional combined with the Lee–Yang–Parr correlation functional (B3LYP)[37–40] with the standard 6-31G(d) basis set.[41] Frequency calculations were performed at the same level of theory to confirm that each stationary point was a local minimum (with zero imaginary frequency) or a transition state (with one imaginary frequency). Single-point calculations were executed at the same level of theory, considering the dispersion correction (dft-D)[42] with a polarizable continuum model (PCM)[43] in THF medium (ε = 7.4257) employing the B3LYP/6-31G(d)-optimized geometries. All DFT calculations were performed with the Gaussian 09 suite of programs.[44]

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